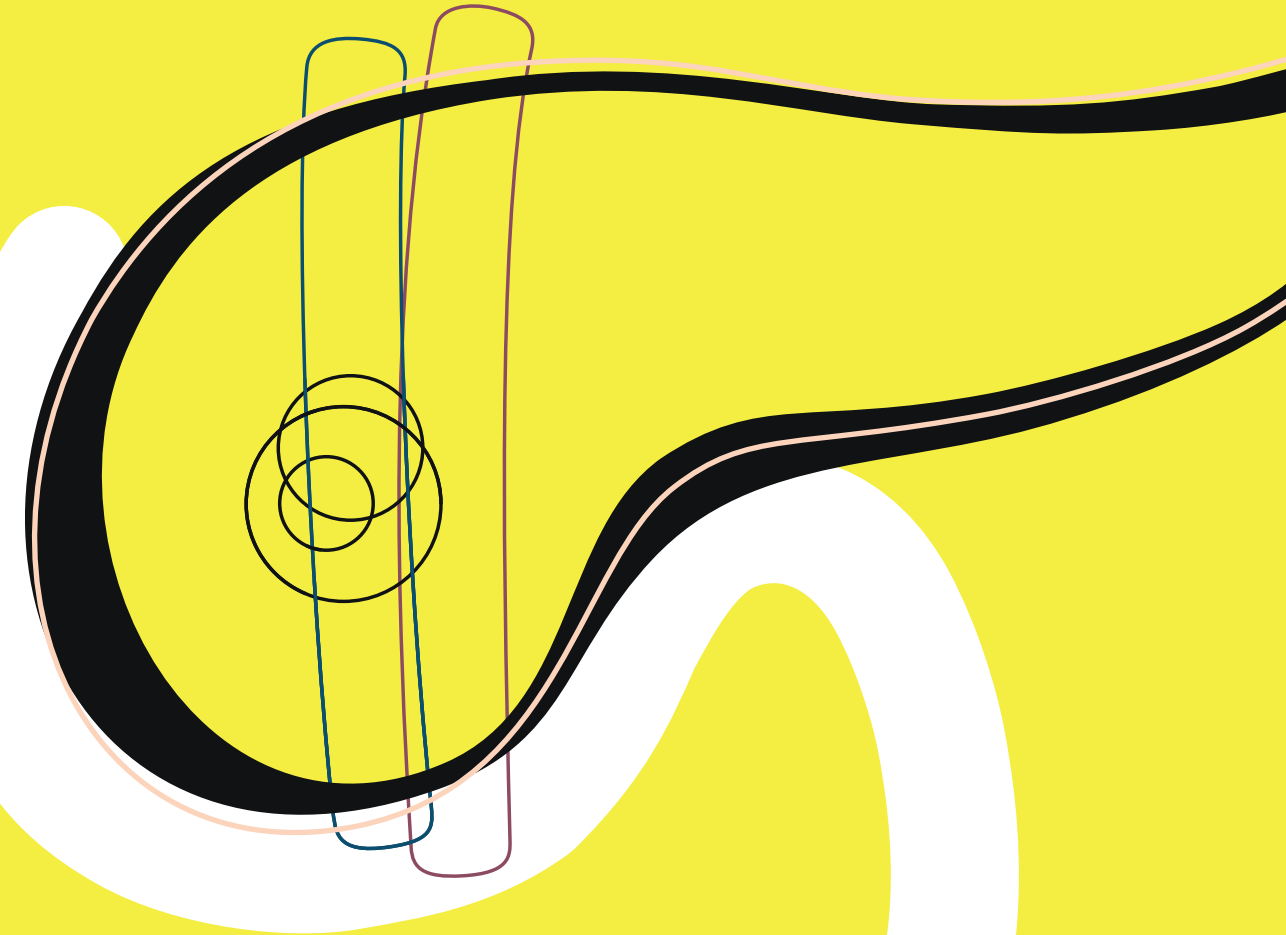
Marieke Walma



Locally Advanced Pancreatic Cancer

Exploring treatment strategies

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Marieke Suzanne Walma

Locally advanced pancreatic cancer: exploring treatment strategies
PhD thesis, Utrecht University, the Netherlands

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Locally Advanced Pancreatic Cancer

Exploring treatment strategies

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(met een samenvatting in het Nederlands)

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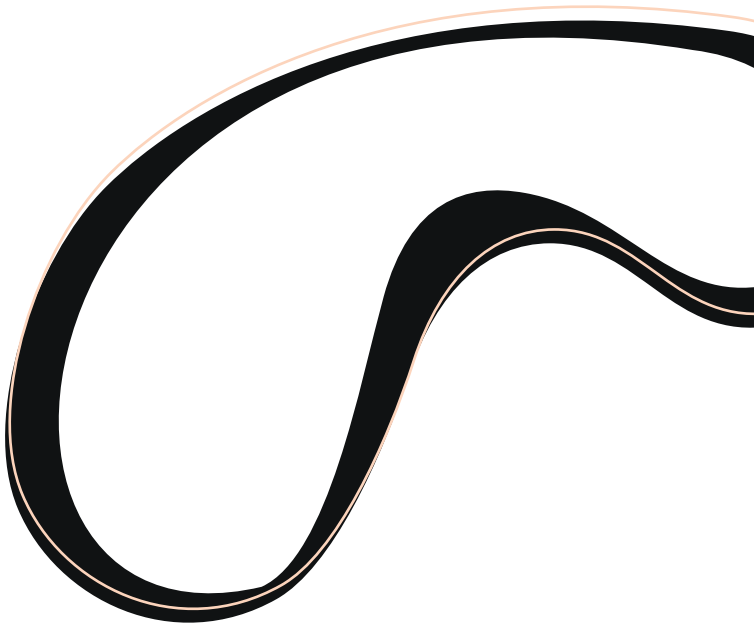


GENERAL INTRODUCTION

The pancreas is a gland located in the upper abdomen with an exocrine and endocrine function. Acinar cells produce digestive enzymes, that are carried to the intestine by pancreatic ducts (exocrine function). The islets of Langerhans produce insulin and glucagon regulating blood glucose levels (endocrine function).[1] Anatomically, the pancreas is surrounded by several important vascular structures. The splenic vein runs posterior to the body and tail of the pancreas and merges with the superior mesenteric vein that crosses posterior to the neck of the pancreas and drains blood from the intestine. Together, they form the portal vein. The celiac trunc arises from the aorta just cranial of the pancreas and gives rise to the splenic and hepatic artery. Caudal from the celiac trunc, just posterior to the lower part of the pancreatic body, the superior mesenteric artery originates from the aorta supplying the organs of the midgut with arterial blood (Figure 1).

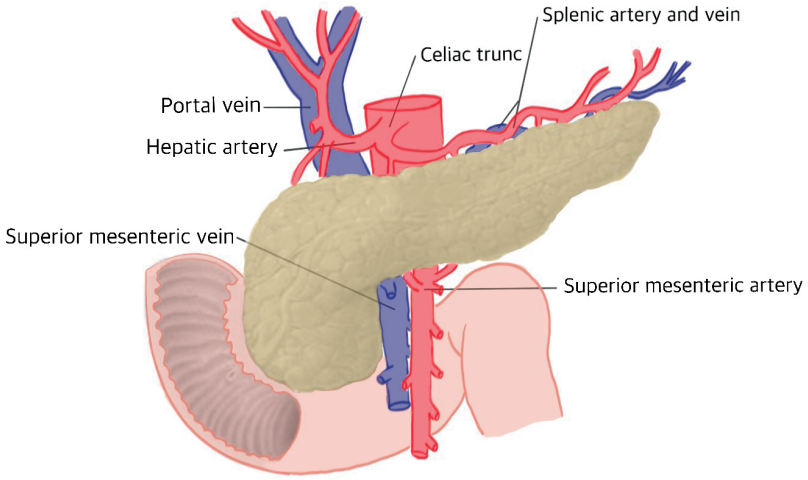


Figure 1. The pancreas with surrounding structures

Diseases of the pancreas can be benign, premalignant, and malignant and originate from different pancreatic cell types. Acute and chronic pancreatitis and a variety of pancreatic cysts are the main benign diseases. The most common premalignant conditions of the pancreas are: intraductal papillary mucinous neoplasms (IPMN), mucinous cystic neoplasms and solid pseudopapillary neoplasms.[1] Malignant diseases of the pancreas can have an endocrine or exocrine origin. Exocrine pancreatic cancer, arising from the pancreatic duct cells, is by far the most common type of malignancy of the pancreas with about 95% of pancreatic cancer being ductal adenocarcinomas.[2]

Pancreatic cancer

With a worldwide incidence of approximately 496,000 new cases and 466,000 deaths in 2020, pancreatic cancer is among the most deadliest of cancers.[3] Due to the increasing incidence and limited treatment options, pancreatic cancer is estimated to become the number two leading cause of cancer-related death in 2030.[4,5] Patients with pancreatic cancer are often staged according to the extent of disease at diagnosis. Inherent to the anatomical position of the pancreas, together with a lack of screening tools, the majority of patients present with an advanced stage of cancer. Only 10-20% of patients are diagnosed with resectable or borderline resectable disease.[6,7] For those patients, surgery combined with adjuvant chemotherapy is the standard of care with a 5-year survival rate of 20%.[6] A recent randomized controlled trial showed a significant improvement with a median overall survival of 54 months in selected patients treated with adjuvant FOLFIRINOX chemotherapy.[8] Currently, neoadjuvant treatment strategies are subject of investigation for patients with (borderline) resectable pancreatic cancer.[9]

Approximately 50-60% of patients with pancreatic cancer have metastases at diagnosis. Another 30-40% present with extensive vascular involvement and are defined as patients with locally advanced pancreatic cancer (LAPC).[4,7] For those, a peri-operative morbidity of 54% and a mortality rate of 12% was described when extended upfront resections were performed. Taken this into account, together with a high recurrence rate and no proven survival benefit, an upfront resection is not deemed beneficial for patients with LAPC.[10,11]

Locally advanced pancreatic cancer

Worldwide, various criteria for LAPC are used.[12-15] According to the Dutch Pancreatic Cancer Group criteria, patients with a tumor exceeding 90 degrees of contact with the celiac trunc, superior mesenteric artery or hepatic artery are defined as LAPC. In addition, a tumor with more than 270 degrees of involvement of the portomesenteric veins is defined as LAPC (Figure 2).[12] National Comprehensive Cancer Network (NCCN) criteria define a tumor with >180° of arterial contact or unreconstructable venous involvement as unresectable.[14]

Historically, patients with LAPC were treated as patients with metastases, in whom systemic chemotherapy is the standard of care. Both were grouped together as 'advanced pancreatic cancer', since surgical resection was not considered a treatment option. In 1997, gemcitabine was shown to give a benefit in quality of life in patients with advanced pancreatic cancer and became the standard of care.[16] Randomized controlled trials including patients with LAPC showed a median survival of 10-12 months when treated with gemcitabine monotherapy.[17,18] In 2011, Conroy *et al.* published a randomized controlled trial showing the superiority of FOLFIRINOX (a combination of

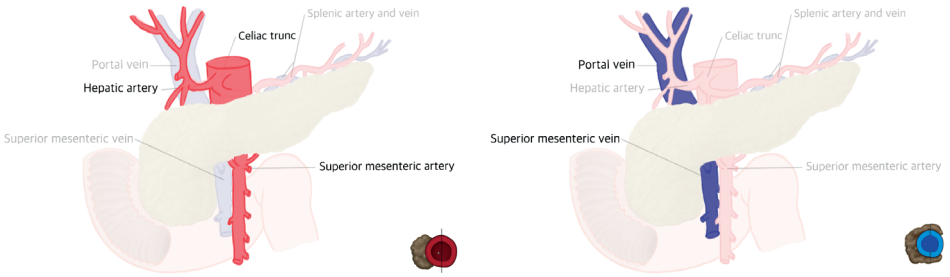


Figure 2. Schematic view of Dutch Pancreatic Cancer Group Criteria for LAPC: >90° of contact with celiac trunc, superior mesenteric artery or hepatic artery (left) or >270° of contact with the portomesenteric vein (right)

5-fluorouracil, oxaliplatin, irinotecan and leucovorin) in patients with metastatic pancreatic cancer when compared to gemcitabine monotherapy, with a median overall survival of 11.1 versus 6.8 months.[19] More recently, nab-paclitaxel plus gemcitabine was reported as being beneficial when compared to gemcitabine monotherapy in patients with metastatic disease with a median overall survival of 8.7 versus 6.6 months.[20] Although these randomized controlled trials included only relatively young and fit patients with distant metastases, the regimen became generally accepted as treatment for patients with locally advanced pancreatic cancer.[21] Observational studies focusing specifically on patients with LAPC, report an overall survival of 24 months for selected patients after FOLFIRINOX and 19 months with nab-paclitaxel/gemcitabine.[22,23] Within these studies, patients often received multimodal treatment with subsequent (chemo) radiotherapy or resection. Proportions and protocols of these subsequent treatments varied considerably. Moreover, studies are mostly from large expert centers and subject to referral and selection bias. This complicates the translation of these results into daily clinical practice. The uncertain external validity of these results impedes shared decision making for the individual patient with LAPC. With this reason part I of this thesis aims to review treatment strategies and clinical outcomes in patients with LAPC reflecting current clinical practice.

Resection of LAPC after chemotherapy

With the introduction of FOLFIRINOX chemotherapy an increased response rate was seen when compared to gemcitabine chemotherapy. Due to response of the tumor to chemotherapy, patients in whom the tumor was initially deemed unresectable could undergo a surgical resection after FOLFIRINOX chemotherapy.[4] Hereby, LAPC became a different entity from metastatic disease. Where previously treatment was aiming for palliation, now a surgical resection became part of the treatment options. Experienced centers also started tumor exploration for patients with stable disease after

chemotherapy and resection rates of approximately 25% are described.[23] Although debate remains whether this is truly an effect of the resection, an encouraging overall survival ranging from 22-35 months has been described for these patients.[24,25] Since FOLFIRINOX is a relatively toxic chemotherapy regimen, it is important to know which patients will benefit from the regimen in terms of survival and/or conversion to resectable disease. Until now this is not yet clear.

Moreover, restaging after treatment with chemotherapy is challenging.[26] RECIST criteria are used to classify the cancer as in regression, stable or progressive.[27] However, RECIST criteria were developed for solid tumors in general. Therefore, the validity of RECIST criteria for patients with irregular, perivascular growing pancreatic cancer is unclear. In addition, studies showed the inability of a CT-scan to differentiate between active tumor tissue and post chemotherapy fibrosis in patients with pancreatic cancer.[28] This complicates the evaluation of post-chemotherapy response, which is the basis whether to proceed to a surgical exploration with the intention for resection. Nevertheless, since there are no other selection tools at hand, the clinical condition of the patient, together with the CT-scan and serum tumor markers (e.g. CA19-9) will determine the advice of a multidisciplinary team to proceed to surgery or not.

Part II of this thesis covers the investigation of diagnostic and predictive tools to select patients who will benefit from chemotherapy or will be eligible for a resection.

Local ablative therapies in LAPC

The majority of patients with LAPC will not undergo a surgical resection despite RECIST stable disease following several months of chemotherapy. Treatment strategies aiming for local tumor control have become a subject of interest. A previous review on local therapies for patients with LAPC showed that radiofrequency ablation (RFA) and irreversible electroporation (IRE) are associated with promising results.[29]

RFA is a thermal-based technique aiming for tumor ablation by frictional heat, applied with a high frequency alternating current through one or more electrodes implanted into the tumor. It is widely used in different kind of solid tumors, such as in the liver, kidney and lung.[30] RFA for LAPC is essentially a form of debulking rather than total tumor ablation, since otherwise nearby vital structures are at risk. When RFA was performed in a multimodal setting, combined with chemo(radio)therapy, a survival of 26–34 months was reported from single center observational studies.[31] IRE is considered a non-thermal technique that applies high voltage electrical pulses between electrodes surrounding the tumor, leading to apoptosis of tumor cells.[32] An overall survival up to 27 months has been reported for patients with LAPC treated with IRE after chemotherapy.[33]

Although no randomized controlled trial has reported these ablative therapies to be superior to systemic treatment only, they are currently increasingly applied in patients with LAPC. Part III of this thesis aims to investigate the applicability of IRE and RFA and explores the safety of RFA in patients with LAPC in preparation for a randomized controlled trial: the PELICAN trial.

In summary, over the last years more treatment strategies have become available for patients with LAPC and overall survival has improved. However, most studies in LAPC are observational and often subject to bias, so that it is unclear how published results translate to clinical practice. This thesis will present clinical outcomes that reflect current clinical practice, will investigate tools to improve patient selection for different (multimodal) treatment strategies and prepares for a randomized controlled trial investigating the efficacy of radiofrequency ablation combined with chemotherapy in patients with LAPC.

THESIS OUTLINE

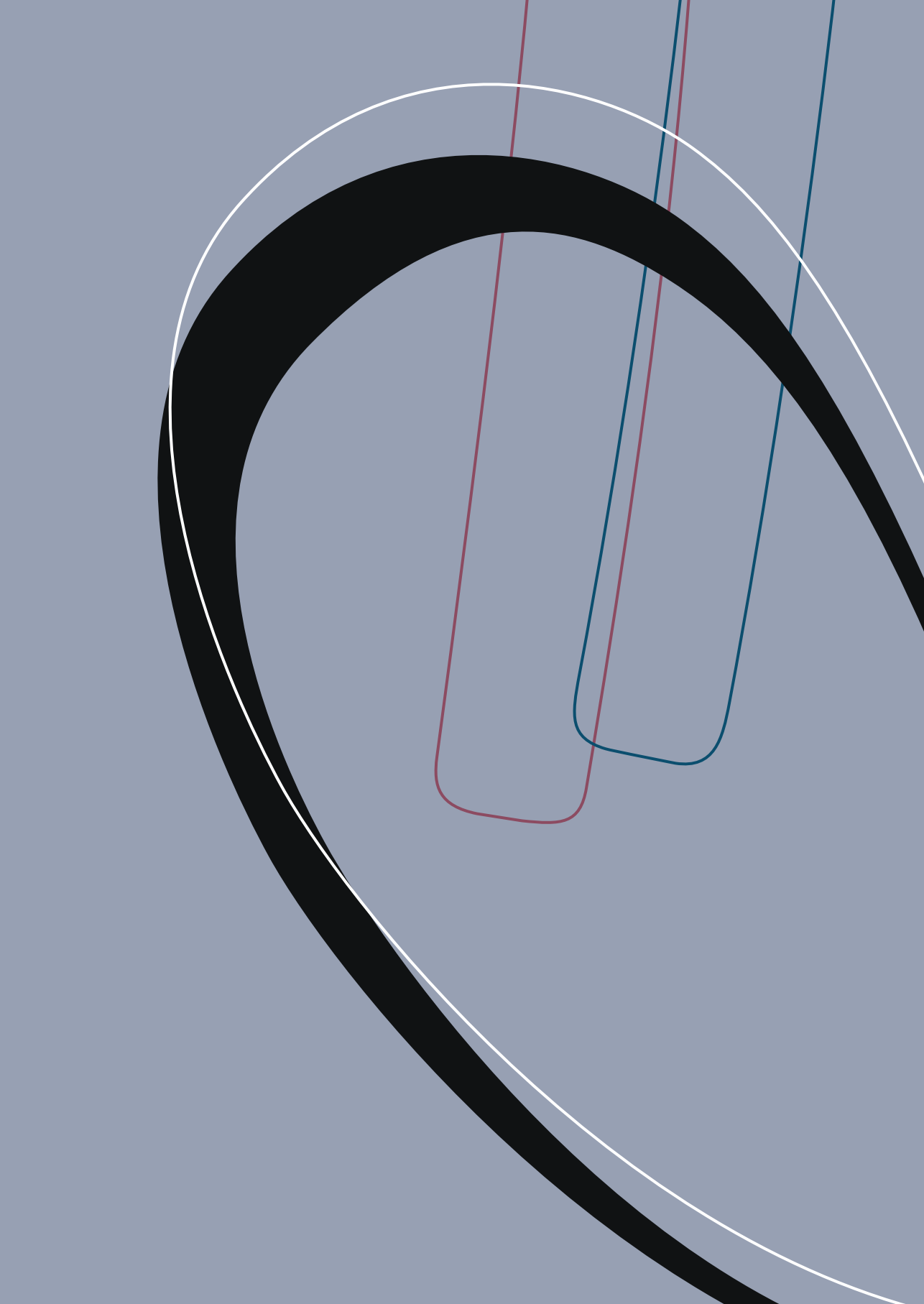
The research questions that are addressed in this thesis are:

Part I	**Current treatment strategies**
Chapter 2	What are the clinical outcomes in published studies on FOLFIRINOX-based therapy in patients with LAPC?
Chapter 3	What are the current treatment strategies and outcomes in a nationwide cohort of consecutive patients with LAPC?
Chapter 4	Is the age of patients with LAPC associated with treatment strategy and overall survival?
Part II	**Outcome prediction**
Chapter 5	What are predictors for overall survival and resection in patients with LAPC at the start of treatment with FOLFIRINOX?
Chapter 6	Does intra-operative ultrasound contribute in selecting patients with LAPC for a surgical resection following FOLFIRINOX chemotherapy?
Chapter 7	What are preoperative clinical predictors of occult metastases during explorative laparotomy in patients with presumed (borderline) resectable pancreatic cancer?
Part III	**Local ablative therapies**
Chapter 8	What are the eligibility criteria for IRE and RFA and what is the extent of overlap or exclusiveness in eligibility for RFA and IRE in patients with LAPC?
Chapter 9	Is RFA a safe treatment strategy for patients with LAPC?
Chapter 10	Does the combination of chemotherapy and RFA improves overall survival in patients with LAPC when compared to chemotherapy alone?

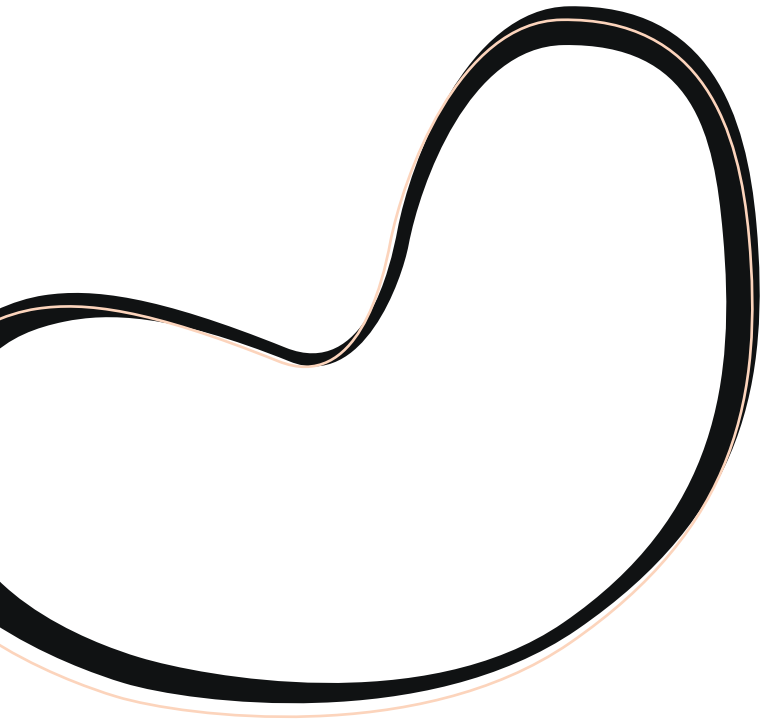
REFERENCES

1. Simeone DM, Pandol SJ. The Pancreas: Biology, diseases, and Therapy. Gastroenterology 2013;144(6):1163-1165.
2. Pancreatic Cancer UK. Published 2018. Accessed July 13, 2020. https://www.pancreaticcancer.org.uk/types
3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209-249.
4. Latenstein AEJ, van der Geest LGM, Bonsing BA, et al. Nationwide trends in incidence, treatment and survival of pancreatic ductal adenocarcinoma. *Eur J Cancer*. 2020;125:83-83. doi:10.1016/j.ejca.2019.11.002
5. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: The unexpected burden of thyroid, liver, and pancreas cancers in the united states. *Cancer Res*. 2014;74(11):2913-2921. doi:10.1158/0008-5472.CAN-14-0155
6. Mizrahi JD, Surana R, Valle JW, Shroff RT. Pancreatic cancer. *Lancet*. 2020;395:2008–20. doi:10.1016/S0140-6736(20)30974-0
7. Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. *Lancet*. 2011;378(9791):607-620. doi:10.1016/S0140-6736(10)62307-0.Pancreatic
8. Conroy T, Hammel P, Hebbar M, Abdelghani MB et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med. 2018.;20;379(25):2395-2406.
9. Versteijne E, Suker M, Groothuis K, Akkermans-Vogelaar JM et al. Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer: results of the dutch randomized phase III PREOPANC trial. J Clin Oncol. 2020 1;38(16):1763-1773.
10. Hernandez J, Mullinax J, Clark W, et al. Survival after pancreaticoduodenectomy is not improved by extending resections to achieve negative margins. *Ann Surg*. 2009;250(1):76-80. doi:10.1097/SLA.0b013e3181ad655e
11. Mollberg N, Rahbari NN, Koch M, et al. Arterial resection during pancreatectomy for pancreatic cancer: A systematic review and meta-analysis. *Ann Surg*. 2011;254(6):882-893. doi:10.1097/SLA.0b013e31823ac299
12. Dutch Pancreatic Cancer Group. Definitions of resectability pancreatic cancer. Published 2012. Accessed March 13, 2019. http://www.dpcg.nl/richtlijnen-classificaties/dpcg-definities.html
13. Isaji S, Mizuno S, Windsor JA, et al. International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. *Pancreatology*. Published online 2018. doi:10.1016/j.pan.2017.11.011
14. Tempero MA, Malafa MP, Al-Hawary M, et al. Pancreatic adenocarcinoma, version 2.2017: Clinical practice guidelines in Oncology. *JNCCN J Natl Compr Cancer Netw*. 2017;15(8):1028-1061. doi:10.6004/jnccn.2017.0131
15. Bockhorn M, Uzunoglu FG, Adham M, et al. Borderline resectable pancreatic cancer: A consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). *Surg (United States)*. Published online 2014. doi:10.1016/j.surg.2014.02.001
16. Burris HA, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomized trial. *J Clin Oncol*. 1997;15(6):2403-2413. doi:10.1200/JCO.1997.15.6.2403
17. Lima CMR, Green MR, Rotche R, et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. *J Clin Oncol*. 2004;22(18):3776-3783. doi:10.1200/JCO.2004.12.082
18. Louvet C, Labianca R, Hammel P, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: Results of a GERCOR and GISCAD phase III trial. *J Clin Oncol*. 2005;23(15):3509-3516. doi:10.1200/JCO.2005.06.023
19. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364(19):1817-1825. doi:10.1056/NEJMoa1011923
20. Goldstein D, El-Maraghi RH, Hammel P, et al. Nab-paclitaxel plus gemcitabine for metastatic pancreatic cancer: Long-term survival from a phase III trial. *J Natl Cancer Inst*. 2015;107(2). doi:10.1093/jnci/dju413
21. Reames BN, Blair AB, Krell RW, et al. Management of Locally Advanced Pancreatic Cancer: Results of an International Survey of Current Practice. *Ann Surg*. Published online 2019. doi:10.1097/SLA.0000000000003568
22. Philip PA, Lacy J, Portales F, et al. Nab-paclitaxel plus gemcitabine in patients with locally advanced pancreatic cancer (LAPACT): a multicentre, open-label phase 2 study. *Lancet Gastroenterol Hepatol*. 2020;5(3):285-294. doi:10.1016/S2468 1253(19)30327-9

23. Suker M, Beumer BR, Sadot E, et al. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. *Lancet Oncol*. 2016;17(6):801-810. doi:10.1016/S1470-2045(16)00172-8
24. Gemenetzis G, Groot VP, Blair AB, et al. Survival in Locally Advanced Pancreatic Cancer After Neoadjuvant Therapy and Surgical Resection. *Ann Surg*. 2019;epublished:doi.10.1097/SLA.0000000000002753. doi:10.1097/SLA.0000000000002753
25. Rangelova E, Wefer A, Persson S, et al. Surgery Improves Survival After Neoadjuvant Therapy for Borderline and Locally Advanced Pancreatic Cancer. *Ann Surg*. Published online 2019:1. doi:10.1097/SLA.0000000000003301
26. Herman J, Ko AH, Komanduri S, et al. Pancreatic Adenocarcinoma, Version 2.2017 Clinical Practice Guidelines in Oncology NCCN Categories of Evidence and Consensus. *JNCCN-Journal Natl Compr Cancer Netw* |. 2017;15(8):1028-1061. doi:10.6004/jnccn.2017.0131
27. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247. doi:10.1016/j.ejca.2008.10.026
28. Ferrone CR, Marchegiani G, Hong TS, et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. *Ann Surg*. 2015;261(1):12-17. doi:10.1097/SLA.0000000000000867
29. Rombouts SJE, Vogel JA, Van Santvoort HC, et al. Systematic review of innovative ablative therapies for the treatment of locally advanced pancreatic cancer. *Br J Surg*. 2015;102(3):182-193. doi:10.1002/bjs.9716
30. Paiella S, Salvia R, Girelli R, et al. Role of local ablative techniques (Radiofrequency ablation and Irreversible Electroporation) in the treatment of pancreatic cancer. *Updates Surg*. 2016;68(3):307-311. doi:10.1007/s13304-016-0385-9
31. Cantore M, Girelli R, Mambrini A, et al. Combined modality treatment for patients with locally advanced pancreatic adenocarcinoma. *Br J Surg*. 2012;99(8):1083-1088. doi:10.1002/bjs.8789
32. Davalos R V., Mir LM, Rubinsky B. Tissue ablation with irreversible electroporation. *Ann Biomed Eng*. 2005;33(2):223-231. doi:10.1007/s10439-005-8981-8
33. Leen E, Picard J, Stebbing J, Abel M, Dhillon T, Wasan H. Percutaneous irreversible electroporation with systemic treatment for locally advanced pancreatic adenocarcinoma. *J Gastrointest Oncol*. Published online 2018. doi:10.21037/jgo.2018.01.14



PART I
Current treatment strategies



Chapter 2

Systematic review of resection rates and clinical outcomes after FOLFIRINOX-based treatment in patients with locally advanced pancreatic cancer

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ABSTRACT

Background

FOLFIRINOX prolongs survival in patients with metastatic pancreatic cancer and may also benefit patients with locally advanced pancreatic cancer (LAPC). Furthermore, it may downstage a proportion of LAPC into (borderline) resectable disease, however data are lacking. This review assessed outcomes after FOLFIRINOX-based therapy in LAPC.

Methods

The PubMed, EMBASE and Cochrane library databases were systematically searched for studies published to 31 August 2015. Primary outcome was the (R0) resection rate.

Results

Fourteen studies involving 365 patients with LAPC were included; three studies administered a modified FOLFIRINOX regimen. Of all patients, 57% (n=208) received radiotherapy. The pooled resection rate was 28% (n=103, 77% R0), with a perioperative mortality of 3% (n=2), and median overall survival ranged from 8.9 to 25.0 months. Survival data after resection were scarce, with only one study reporting a median overall survival of 24.9 months in 28 patients. A complete pathologic response was found in 6 of 85 (7%) resected specimens. Dose reductions were described in up to 65% of patients, grade 3-4 toxicity occurred in 23% (n=51) of patients, and 2% (n=5) had to discontinue treatment. Data of patients treated solely with FOLFIRINOX, without additional radiotherapy, were available from 292 patients: resection rate was 12 % (n=29, 70% R0), with 15.7 months median overall survival and 19% (n=34) grade 3–4 toxicity.

Conclusions

Outcomes after FOLFIRINOX-based therapy in patients with LAPC seem very promising but further prospective studies are needed, especially with regard to survival after resection.

INTRODUCTION

Pancreatic ductal adenocarcinoma has very poor survival rates. Surgical resection with adjuvant chemotherapy offers the best survival but is only feasible in approximately 20% of patients.[1] Forty percent of patients present without distant metastases but with extensive vascular involvement prohibiting upfront resection, known as locally advanced pancreatic cancer (LAPC).[1] In these patients, gemcitabine monotherapy (sometimes combined with radiotherapy) has been the standard palliative treatment for decades. Unfortunately, response rates are low without clear improvement in survival.[2]

Recently, the superiority of FOLFIRINOX, a combination of 5-fluorouracil, oxaliplatin, irinotecan and leucovorin, over gemcitabine monotherapy in patients with metastatic pancreatic cancer was demonstrated: a response rate of 31.6 versus 9.4 % and a median overall survival of 11.1 months versus 6.8 months ($p < 0.001$) has been observed.[3] The comparable poor prognosis of LAPC and the lack of beneficial therapies have also led to the administration of FOLFIRINOX, sometimes combined with radiotherapy, in patients with LAPC; however, no randomized trials have been conducted on this topic.

Several observational studies on FOLFIRINOX-based treatment included both patients with LAPC and borderline resectable pancreatic cancer. Borderline resectable disease is defined by the National Comprehensive Cancer Network (NCCN) as an arterial involvement of less than 180 degrees or a venous involvement with options for reconstruction.[4] The inclusion of patients with borderline resectable pancreatic cancer may positively influence outcomes as these patients have a higher chance of resection in advance. Therefore, the aim of this study was to evaluate the results of FOLFIRINOX-based treatment only in patients with LAPC, considering (R0) resection rate as the primary outcome.

METHODS

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[5]

Search and selection

The PubMed, EMBASE, and Cochrane Library databases were systematically searched for studies published from 2005 to 31 August 2015. Duplicates were removed and studies published in languages other than English were excluded. Three authors (MW, SR, JV) independently screened articles by title and abstract and, if applicable, the full

articles for eligibility based on predefined inclusion and exclusion criteria. Discordant judgments were addressed by consulting a fourth author (LR). The reference lists of all included papers were searched manually to identify missed, but potentially relevant, studies.

Eligibility criteria

Retrospective and prospective studies on FOLFIRINOX in patients with LAPC, reporting (R0) resection rate, survival, response rate or toxicity, were eligible for inclusion in our study. Conference abstracts or case reports (i.e. sample size of fewer than five patients) were excluded.

Assessment of methodological quality

The level of evidence was classified and a classical risk of bias assessment was applied for all included studies according to the Oxford Centre for Evidence-Based Medicine (CEBM) Critical Appraisal Skills Programme (CASP) 2004.[6,7]

Data collection

Study design, study population, sample size, resectability criteria and treatment regimen were extracted from the included studies. Primary outcome was the (R0) resection rate. Secondary outcomes were postoperative complications, pathological response, overall survival, response rate, CA19-9 response, and toxicity. In addition, if FOLFIRINOX treatment was followed by radiotherapy,
outcomes during FOLFIRINOX administration before the start of radiotherapy were additionally extracted to get more insight into the outcome for solely FOLFIRINOX treatment. Corresponding authors were approached when data were missing or could not be extracted from the article, or if no data were presented for the LAPC population separately.

Statistical analysis

Overall (R0) resection rate, postoperative complications, complete pathologic response, response rate, CA19-9 response, and toxicity were calculated. A meta-analysis of overall survival was not performed because of substantial heterogeneity between studies and lack of individual patient data.

RESULTS

Fourteen studies involving 365 patients (one prospective observational study[10] and 13 retrospective studies[8,9,11–21]) were included (Figure 1). No randomized trials were

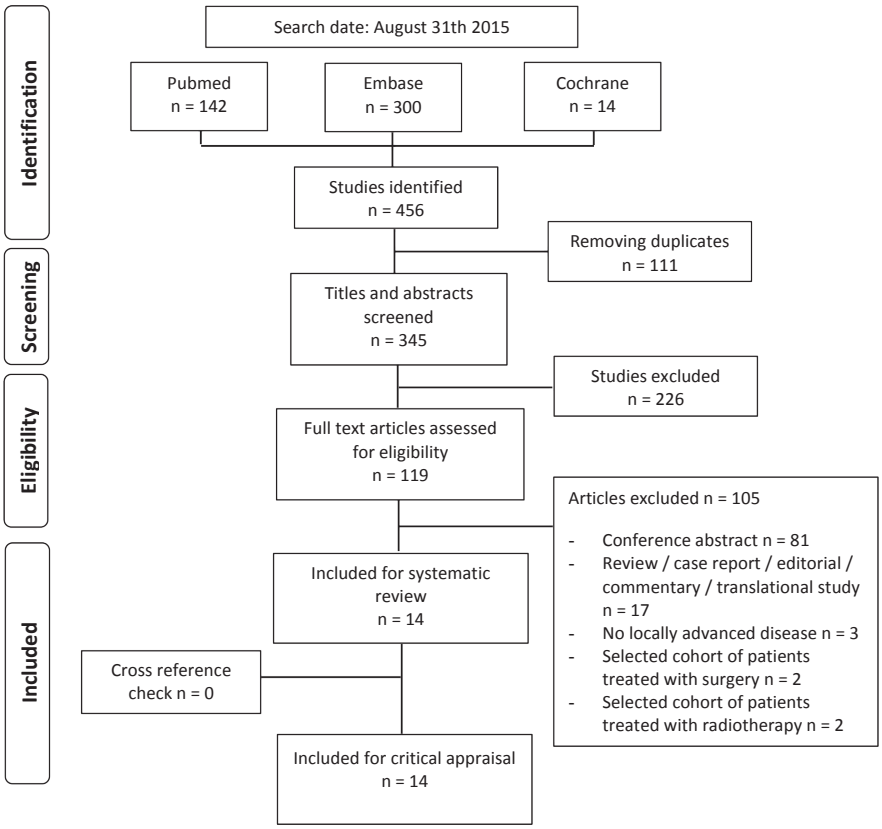

Figure 1. Study selection process

available. LAPC was defined according to the National Comprehensive Cancer Network (NCCN) (n=4),[4,11,12,18,21] the consensus statement of the American Hepato-Pancreato-Biliary Association [AHPBA/SSAT/SSO] (n=3),[8,9,14,22] or based on consensus within the multidisciplinary team (n=2).[10,17] Five articles did not define LAPC,[13,15,16,19,20] and all studies had a substantial risk of bias (Table 1).

Treatment regimen

FOLFIRINOX was administered as single treatment in four studies[10,12,13,15] and combined with radiotherapy in 10 studies.[8,9,11,14,16–21] Three of the 14 studies administered a modified FOLFIRINOX regimen from the beginning of therapy by eliminating the bolus of fluorouracil,[16] in addition to lowering the dose of irinotecan,[8] or by a starting dose of 80% of the intensity of the FOLFIRINOX regimen.[21] One study administered a modified regimen in 68% of all first cycles.[20] In the remaining 10 studies, FOLFIRINOX was

administered as per the PRODIGE 4/ACCORD 11 trial protocol at the start, but also reported on a dose-reduction during the course of treatment for 63 % of total cycles and in up to 65% of patients.[3,9–15,17–19] The median number of cycles was reported in five studies and ranged from four to eight.[8,11,17,20,21] Five studies reported FOLFIRINOX to be first-line treatment.[12,14,15,17,21] Patients who had progression under FOLFIRINOX treatment and subsequent radiotherapy were treated with second-line chemotherapy in two studies.[17,21] After resection, adjuvant gemcitabine-based chemotherapy was reported by two studies, as well as additional combined chemoradiotherapy by one study.[8,14,15] The remaining seven studies did not reported on prior, second-line, or adjuvant therapy.[9,10,13,16,18–20]

Overall, 208 of 362 patients (57%) were treated with additional radiotherapy after FOLFIRINOX treatment (Table 2). Radiotherapy was delivered through conventional treatment,[8,11,14] intensity-modulated radiation therapy (IMRT),[16,17,19,21] or as stereotactic body radiation therapy (SBRT).[9,18] One study did not report on the details of radiotherapy.[20] Radiation was combined with chemotherapy in six studies.[8,11,14,16,19,21] The chemosensitizer, as part of the chemoradiation, differed between gemcitabine, capecitabine, 5-fluorouracil, or a combination. The total administered dose of radiotherapy ranged from 36 to 54 Gy, given in fractions ranging from 3 to 30. Three studies did not report on the dosage of radiotherapy.[16,20,21]

Resection rate and postoperative outcomes

Each of the 14 studies reported on resection rates, with a total of 28% (n=103) after a median of five to eight cycles of FOLFIRINOX and additional radiotherapy in 66% of patients (56 of 85 patients with available data) (Table 2).[9,10,12–18,20,21] Of these, 10 studies reported a total R0 resection rate of 77% (n=72).[8,9,11,14–19,21] Morbidity after resection was reported in three studies including 64 patients, and ranged from 20% grade 3–4 to 60% overall complications.[11,17,21] Morbidity was specified for 33 patients, with postoperative infection (n=5) and bleeding (n=3) as the most common cause. Pancreatic fistula was reported in one patient, and median hospital stay ranged from 6 to 7 days.[11,21] Perioperative mortality, reported by five studies, was 3% (n=2).[8,9,17,18,21] In total, 6 of 85 (7%) resection specimens showed a complete pathologic response (Table 2).[8,11,12,15,17–19,21]

One study compared patients who proceeded to surgery with those who did not (n=31 and n=70, respectively). Hepatic artery and unreconstructable venous involvement were more common in the group that proceeded to resection compared with celiac trunk, superior mesenteric artery, or multiple vessel involvement (p=0.001).[21] Another study did not reach significance when comparing arterial involvement with venous involvement in resected patients.[17] No studies specified vascular involvement in degrees.

Table 1. Risk of bias assessment

Author	Level of evidence[a]	Criteria for LAPC	Clear in- and exclusion criteria	Risk of selection bias	Standardized intervention	Standardized treatment[b]	Standardized outcome	Confounding factors	Missing data verified	Duration of follow up > 12 months	Lost to follow up
Blazer et al.[8]	2b	AHPBA/SSO/SSAT	+	+	+	+	+/-	+	+	+	+
Boone et al.[9]	2b	AHPBA/SSO/SSAT	+	+	NR	+/-	+/-	+	NR	-	+
Conroy et al.[10]	2b	MDT	+/-	+/-	+	+/-	+	+	+/-	+	NR
Faris et al.[11]	2b	NCCN	+	+	+	+/-	+/-	+	+/-	+	NR
Gunturu et al.[12]	2b	NCCN	+	+	+	+/-	+/-	+	NR	+	NR
Hohla et al.[13]	2b	NR	+/-	+	+	+/-	+/-	+	NR	-	NR
Hosein et al.[14]	2b	AHPBA/SSO/SSAT	+	+	+	+	+/-	+	NR	+	NR
Kraemer et al.[15]	2b	NR	+/-	+	+	-	-	+	NR	-	NR
Mahaseth et al.[16]	2b	NR	+/-	+	+	-	+	+/-	NR	+	+
Marthey et al.[17]	2b	MDT	+/-	+	+	+/-	+	+/-	NR	+	NR
Mellon et al.[18]	2b	NCCN	+	+	+	+	+	NR	+	-	NR
Moorcraft et al.[19]	2b	NR	+/-	+	+	-	+	+/-	NR	+	NR
Peddi et al.[20]	2b	NR	+/-	+	+	-	+	+/-	+	+	NR
Sadot et al.[21]	2b	NCCN	+	+	+	+	+	+/-	+	+	NR

[a]According to the Oxford CEBM levels of evidence[6], [b]Concerning pre- and post-interventional treatments; AHPBA/SSO/SSAT: American Hepato-Pancreato-Biliary Association, Society for Surgery of Alimentary Tract, Society of Surgical Oncoloy[22]; +:yes; -:no; +/-: partially; NR not reported; MDT multidisciplinary team; NCCN: national comprehensive cancer network[4]

Table 2. Outcomes after FOLFIRINOX-based treatment in patients with LAPC

Author	No. of patients	Treated with radiotherapy	Resection rate	R0 resection rate	Complete pathologic response	Response rate	Median OS (months)	Grade 3-4 toxicity
Blazer et al.[8]	25	15/25 (60)	11/25 (44)	10/11 (91)	0/11 (0)	2/23 (9)[a]	NR	NR
Boone et al.[9]	13[b]	5/10 (50)	2/10 (20)	1/2 (50)	NR	NR	8.9	5/10 (50)
Conroy et al.[10]	11[c]	0 (0)	0/11 (0)	NA	NA	3/11 (27)	15.7	NR
Faris et al.[11]	22	20/22 (91)	5/22 (23)	5/5 (100)	1/5 (20)	8/22 (36)	Nre 3-yr 7%	NR
Gunturu et al.[12]	16	0 (0)	2/16 (13)	NR	0/2 (0)	8/16 (50)	Nre 6-month 94% 12-month 83%	NR
Hohla et al.[13]	6	0 (0)	2/6 (33)	NR	NR	NR	NR	NR
Hosein et al.[14]	14	9/14 (64)	6/14 (43)	5/6 (83)	NR	NR	NR	NR
Kraemer et al.[15]	7	0 (0)	1/7 (14)	0/1 (0)	0/1 (0)	NR	NR	NR
Mahaseth et al.[16]	20	10/20 (50)	4/20 (20)	3/4 (75)	NR	NR	NR	NR
Marthey et al.[17]	77	54/77 (70)	28/77 (36)	25/28 (89)	4/28 (14)	22/77 (28)	21.6	20/77 (26)
Mellon et al.[18]	21	21/21 (100)	5/21 (24)	5/5 (100)	0/5 (0)	NR	NR	NR
Moorcraft et al.[19]	13	7/13 (54)	2/13 (15)	2/2 (100)	1/2 (50)	4/13 (31)	18.4	7/13 (54)
Peddi et al.[20]	19	4/19 (21)	4/19 (21)	NR	NR	NR	Nre	5/19 (26)
Sadot et al.[21]	101	63/101 (62)	31/101 (31)	16/29 (55)[d]	0/31 (0)	29/101 (29)	25	14/101 (14)
Overall	365	208/362 (57)	103/362 (28)	72/93 (77)	6/85 (7)	76/263 (29)		51/220 (23)

Data are expressed as n (%) unless otherwise specified; OS overall survival; NA not applicable; NR not reported; NRE not reached; [a] Two patients died before the restaging scan; [b] Three patients refused treatment or were lost to follow-up; [c] One patient had a local recurrence; [d] Two pathology reports were pending

Eight studies reported the resection rate for solely FOLFIRINOX treatment, without additional radiotherapy, with a pooled resection rate of 12% (n=29).[9,10,12–15,17,21] In addition, four of these studies reported 14 R0 resections (70%) from a total of 20 resections [9,14,15,21] without any complete pathologic response (Table 3).

Median overall survival

The median overall survival was reported in five studies and ranged from 8.9 to 25 months; of these patients, 64% were treated with radiotherapy.[9,10,17,19,21] In three studies, median survival was not reached.[11,12,20] One study showed a 1-year survival of 83%, in which the majority of patients (91%) were treated with radiotherapy.[12] A second study showed a 3-year survival of 7%; none of the patients received radiotherapy (Table 2).[11]

In addition, one study reported a median overall survival of 24.9 months in 28 patients who underwent pancreatic resection.[17] Resection was preceded by radiotherapy in 24 patients. In two other studies, survival data after resection were available from only two patients.[9,19] Only one study treated LAPC patients with solely FOLFIRINOX, without additional radiotherapy or resection, and reported a median overall survival of 15.7 months (Table 3).[10]

Response rate and CA-19.9 response

Seven studies reported on response rates.[8,10–12,17,19,21] Almost all defined response rate as complete or partial response according to Response Evaluation Criteria In Solid Tumors (RECIST) criteria,[11–13,16,17,19–21] and one according to the World Health Organization (WHO) criteria.[10] Of the 238 patients who were treated with FOLFIRINOX, 7% of patients received additional radiotherapy, which led to response rates ranging from 9% (n=2) to 50% (n=8), with a total response rate of 29% (n=76) (Table 2). CA-19.9 reduction was reported in three studies: an overall >30% reduction in 70% of patients, an overall >50% reduction in 54% of patients, and a normalization of the concentration in 35% of all patients.[8,11,17]

In case of solely FOLFIRINOX treatment, response rates ranged from 9% (n=2) to 50% (n=8), with a total of 23% (n=39) (Table 3). Three studies that administered subsequent radiotherapy in selected patients reported response rates before and after radiotherapy, and showed an additional response ranging from 0% (n=0) to 9% (n=9) due to radiotherapy treatment.[8,11,21]

Table 3. Outcomes of solely FOLFIRINOX treatment, including studies reporting data after FOLFIRINOX treatment prior to the start of additional radiotherapy

Author	No. of patients	Resection rate	R0 resection rate	Complete pathologic response	Response rate	Median OS (months)	Grade 3-4 toxicity
Blazer et al.[8]	25	-	-	-	2/23 (9)[a]	NR	NR
Boone et al.[9]	13[b]	2/10 (20)	1/2 (50)	NR	NR	NR	-
Conroy et al.[10]	11[c]	0/11 (0)	NA	NA	3/11 (27)	15.7	NR
Faris et al.[11]	22	-	-	-	6/22 (27)	-	NR
Gunturu et al.[12]	16	2/16 (13)	NR	0/2 (0)	8/16 (50)	Nre 6-month 94% 12-month 83%	NR
Hohla et al.[13]	6	2/6 (33)	NR	NR	NR	NR	NR
Hosein et al.[14]	14	3/14 (21)	2/3 (67)	NR	NR	NR	-
Kraemer et al.[15]	7	1/7 (14)	0/1 (0)	0/1 (0)	NR	NR	NR
Marthey et al.[17]	77	4/77 (5)	-	-	-	-	20/77 (26)
Sadot et al.[21]	101	15/101 (15)	11/14 (79)[d]	0/15 (0)	20/101 (20)	-	14/101 (14)
Overall	292	29/242 (12)	14/20 (70)	0/18 (0)	39/173 (23)		34/178 (19)

OS: overall survival; NR: not reported; NA: not applicable; Nre: not reached; - not reported separately for FOLFIRINOX, only combined with radiotherapy (Table 2); [a] 2 patients died before restaging scan; [b] 3 patients refused treatment or were lost to follow up; [c] 1 patient had a local recurrence; [d] 1 pathology reports was pending

Toxicity

Five studies reported a 23% (n=51) grade 3–4 toxicity, without grade 5 toxicity (Table 2).[9,17,19–21] None of the studies reported specifically on the toxicity caused by radiation. When considering toxicity for FOLFIRINOX alone, two studies reported a total grade 3–4 toxicity rate of 19% (n=34) and no grade 5 toxicity (death) (Table 3).[17,21] The most common grade 3 and 4 complications were neutropenia (10%) and nausea or vomiting (9%).[9,17,19,20] Eight studies reported on discontinuation of treatment due to unacceptable toxicity, with a pooled discontinuation rate of 2% (n=5).[10,11,14,16–18,21]

DISCUSSION

This systematic review on clinical outcomes after FOLFIRINOX-based treatment for LAPC demonstrated a 28% resection rate, of which 77% were R0, and a median overall survival ranging between 8.9 and 25.0 months. Fifty-seven percent of these patients were treated with additional radiotherapy. These data suggest that FOLFIRINOX- based treatment is indeed a promising option for patients with LAPC, with acceptable toxicity (23% grade 3–4 complications). After surgical resection, survival data were lacking as only one study reported a median overall survival of 24.9 months.[17]
One previous review included studies published up to March 2014 and reported resection rates from six studies.[23] The current review, including 14 studies, gives an updated overview and shows other clinical outcomes after FOLFIRINOX treatment specifically in patients with LAPC. As expected, the overall R0 resection rates reported in our review (70–77%) are slightly lower, as reported by two recent studies (84–92%) on borderline resectable disease.[24,25] Surgical outcomes post-resection seem comparable with outcomes in upfront resectable patients, although still based on immature data.[26–28]

Although no study directly compared outcomes after FOLFIRINOX versus gemcitabine monotherapy in LAPC, the results of FOLFIRINOX seem clearly superior to gemcitabine, with reported response rates of 4.2–14.9% and a resection rate of only 7%.[29,30] Moreover, none of the established therapies for LAPC have reported resection rates similar to those of FOLFIRINOX reported in our review.[31]

When addressing toxicity, our review shows remarkable lower toxicity rates compared with the PRODIGE 4/ACCORD 11 trial,[3] which reported 46% grade 3–4 neutropenia compared with 19 % after FOLFIRINOX alone in our review. In the PRODIGE/ACCORD trial, the median number of treatment cycles administered was 10 and the median relative dose intensities of fluorouracil, irinotecan, and oxaliplatin were 82, 81 and 78%, respectively. This suggests that the reduced toxicity rate in our review is probably

explained by the administered modified regimens by start and/or dose reductions during treatment, as described in all included studies.

Our study has some limitations. First, the allocation of FOLFIRINOX was often not based on predefined criteria but at the discretion of the treating team. Therefore it is inevitable that selection bias has occurred. No randomized trials are performed and all studies reported only on patients who actually received (or even completed) FOLFIRINOX treatment. In other words, the percentage of patients with LAPC not receiving FOLFIRINOX treatment and the survival in the entire cohort of LAPC were not reported. Furthermore, only half of the studies reported the guidelines used to establish resectability (Table 1). These guidelines use various definitions.[4,22] Moreover, studies reporting on survival after resection with FOLFIRINOX in LAPC are scarce and immature. Finally, the interventional treatment was not standardized. Different dose reductions and modification schemes were applied and were not performed according to a protocolled reduction schedule, but based on the preference of the treating physician. In addition, the radiotherapy regimens varied between the studies.

An important clinical question is how to decide which patient may benefit from surgical exploration after FOLFIRINOX treatment. A recent study clearly demonstrated that post-FOLFIRINOX CT-based treatment decision making in pancreatic cancer is highly unreliable.[24] In that study, a senior pancreatic surgeon, blinded to FOLFIRINOX treatment, judged 19 of the 40 resected patients as non-resectable based on post-FOLFIRINOX imaging; however, all 40 patients underwent a resection, with a remarkable 92% R0 resection rate and a median overall survival of 35 months for the entire group (19 LAPC and 9 borderline). Several other studies have also recommended an exploratory laparotomy after induction therapy in the absence of disease progression on subsequent imaging.[32,33] These new insights on the low accuracy of CT imaging in the assessment of resectability, and thus the recommendation for surgical exploration after induction, suggest that the resection rates demonstrated in these previously published studies might currently be even higher in expert centers. It is currently unclear whether a different approach should be taken in patients with LAPC compared with these series, which also included patients with borderline resectable disease. Future studies should validate selection criteria for surgical exploration. Improved imaging modalities are urgently needed to improve the post-FOLFIRINOX decision-making process.

This review demonstrates the need for prospective unselected studies with strict definitions, thus including patients not receiving FOLFIRINOX. Such studies should ideally report on consecutive patient (treatment) outcomes, including quality of life, and on the overall survival of all patients, especially those undergoing resection after

FOLFIRINOX. Since a randomized controlled trial comparing FOLFIRINOX with gemcitabine for LAPC seems unethical, future prospective unselected cohort studies are recommended to investigate which patients might be eligible for, and could benefit from, FOLFIRINOX and/or multimodality treatments. Finally, studies should focus on optimizing selection criteria for surgical exploration after FOLFIRINOX in LAPC.[24]

CONCLUSIONS

Outcomes after FOLFIRINOX treatment in patients with LAPC are promising, both for toxicity and (R0) resection rates. Future unselected prospective cohort studies are needed to determine the exact role or FOLFIRINOX in LAPC.

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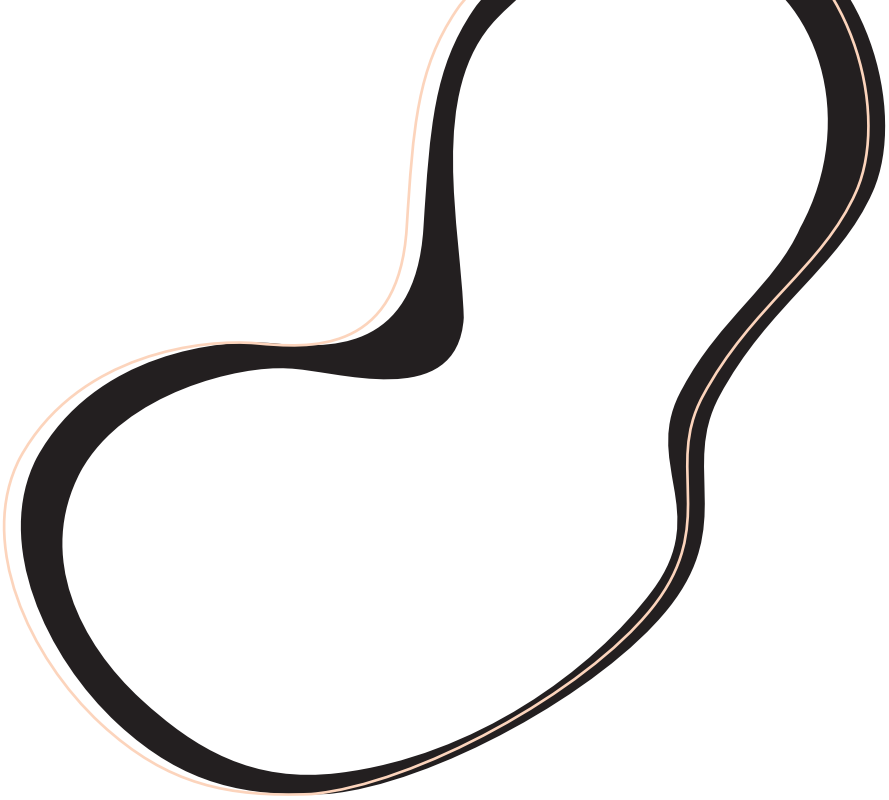
REFERENCES

1. Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. Lancet. 2011;378(9791): 607–20.
2. Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol. 1997;15(6):2403–13.
3. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817–25.
4. National Comprehensive Cancer Network. NCCN guidelines version 2.2015. Pancreatic adenocarcinoma. 2015. http://www.trikobe.org/nccn/guideline/pancreas/english/pancreatic.pdf. Accessed 15 Sep 2015.
5. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010;8(5):336–41.
6. Oxford Centre for Evidence-Based Medicine, Levels of Evidence Working Group. The 2011 OCEBM levels of evidence. 2014. http://www.cebm.net/ocebm-levels-of-evidence/. Accessed 14 Sep 2015.
7. Critical Appraisal Skills Programme. 12 questions to help you make sense of cohort study. Cohort Study Checklist 2013. 2011. http://www.casp-uk.net/#!casp-tools-checklists/c18f8. Accessed 14 Sep 2015.
8. Blazer M, Wu C, Goldberg RM, Phillips G, Schmidt C, Muscarella P, et al. Neoadjuvant modified (m) FOLFIRINOX for locally advanced unresectable (LAPC) and borderline resectable (BRPC) adenocarcinoma of the pancreas. Ann Surg Oncol. 2015;22(4):1153–9.
9. Boone BA, Steve J, Krasinskas AM, Zureikat AH, Lembersky BC, Gibson MK, et al. Outcomes with FOLFIRINOX for borderline resectable and locally unresectable pancreatic cancer. J Surg Oncol. 2013;108(4):236–41.
10. Conroy T, Paillot B, Francois E, Bugat R, Jacob JH, Stein U, et al. Irinotecan plus oxaliplatin and leucovorin-modulated fluorouracil in advanced pancreatic cancer. A Groupe Tumeurs Digestives of the Federation Nationale des Centres de Lutte Contre le Cancer study. J Clin Oncol. 2005;23(6):1228–36.
11. Faris JE, Blaszkowsky LS, McDermott S, Guimaraes AR, Szymonifka J, Huynh MA, et al. FOLFIRINOX in locally advanced pancreatic cancer: the Massachusetts General Hospital Cancer Center experience. Oncologist. 2013;18(5):543–8.
12. Gunturu KS, Yao X, Cong X, Thumar JR, Hochster HS, Stein SM, et al. FOLFIRINOX for locally advanced and metastatic pancreatic cancer: single institution retrospective review of efficacy and toxicity. Med Oncol. 2013;30(1):361.
13. Hohla F, Hopfinger G, Romeder F, Rinnerthaler G, Bezan A, Stattner S, et al. Female gender may predict response to FOLFIRINOX in patients with unresectable pancreatic cancer: a single institution retrospective review. Int J Oncol. 2014;44(1):319–26.
14. Hosein PJ, Macintyre J, Kawamura C, Maldonado JC, Ernani V, Loaiza-Bonilla A, et al. A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma. BMC Cancer. 2012;12:199.
15. Kraemer PC, Schmidt HH, Ladekarl M. Danish experiences with FOLFIRINOX as first-line therapy in patients with inoperable pancreatic cancer. Dan Med J. 2014;61(4):A4819.
16. Mahaseth H, Brutcher E, Kauh J, Hawk N, Kim S, Chen Z, et al. Modified FOLFIRINOX regimen with improved safety and maintained efficacy in pancreatic adenocarcinoma. Pancreas. 2013;42(8):1311–5.
17. Marthey L, Sa-Cunha A, Blanc JF, Gauthier M, Cueff A, Francois E, et al. FOLFIRINOX for locally advanced pancreatic adenocarcinoma: results of an AGEO multicenter prospective observational cohort. Ann Surg Oncol. 2015;22(1):295–301.
18. Mellon EA, Hoffe SE, Springett GM, Frakes JM, Strom TJ, Hodul PJ, et al. Long-term outcomes of induction chemotherapy and neoadjuvant stereotactic body radiotherapy for borderline resectable and locally advanced pancreatic adenocarcinoma. ActaOncol. 2015;54(7):979–85.

19. Moorcraft SY, Khan K, Peckitt C, Watkins D, Rao S, Cunningham D, et al. FOLFIRINOX for locally advanced or metastatic pancreatic ductal adenocarcinoma: the Royal Marsden experience. Clin Colorectal Cancer. 2014;13(4):232–8.
20. Peddi PF, Lubner S, McWilliams R, Tan BR, Picus J, Sorscher SM, et al. Multi-institutional experience with FOLFIRINOX in pancreatic adenocarcinoma. JOP. 2012;13(5):497–501.
21. Sadot E, Doussot A, O'Reilly EM, Lowery MA, Goodman KA, Do RK, et al. FOLFIRINOX induction therapy for stage 3 pancreatic adenocarcinoma. Ann Surg Oncol. 2015;22(11):3512–21.
22. Callery MP, Chang KJ, Fishman EK, Talamonti MS, William Traverso L, Linehan DC. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. Ann Surg Oncol. 2009;16(7):1727–33.
23. Petrelli F, Coinu A, Borgonovo K, Cabiddu M, Ghilardi M, Lonati V, et al. FOLFIRINOX-based neoadjuvant therapy in borderline resectable or unresectable pancreatic cancer: a meta analytical review of published studies. Pancreas. 2015;44(4): 515–21.
24. Ferrone CR, Marchegiani G, Hong TS, Ryan DP, Deshpande V, McDonnell EI, et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer.Ann Surg.2015;261(1):12–7
25. Pietrasz D, Marthey L, Wagner M, Blanc JF, Laurent C, Turrini O, et al. Pathologic major response after FOLFIRINOX is prognostic for patients secondary resected for borderline or locally advanced pancreatic adenocarcinoma: an AGEOFRENCH, prospective, multicentric cohort. AnnSurgOncol.2015;22 Suppl 3:1196–205.
26. Serrano PE, Cleary SP, Dhani N, Kim PT, Greig PD, Leung K, et al. Improved long-term outcomes after resection of pancreatic adenocarcinoma: a comparison between two time periods. Ann Surg Oncol. 2015;22(4):1160–7.
27. Hata T, Motoi F, Ishida M, Naitoh T, Katayose Y, Egawa S, et al. Effect of hospital volume on surgical outcomes after pancreaticoduodenectomy:a systematic review and meta-analysis. AnnSurg.2016;263(4):664-72
28. Pugalenthi A, Protic M, Gonen M, Kingham TP, Angelica MI, Dematteo RP, et al. Postoperative complications and overall survival after pancreaticoduodenectomy for pancreatic ductal adenocarcinoma. J Surg Oncol. 2016;113(2):188–93.
29. Louvet C, Labianca R, Hammel P, Lledo G, Zampino MG, Andre T, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial.
30. Rocha Lima CM, Green MR, Rotche R, Miller WH Jr, Jeffrey GM, Cisar LA, et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. J Clin Oncol. 2004;22(18):3776–83.
31. Conroy T, Bachet JB, Ayav A, Huguet F, Lambert A, Caramella C, et al. Current standards and new innovative approaches for treatment of pancreatic cancer. Eur J Cancer. 2016;57:10–22.
32. Pietryga JA, Morgan DE. Imaging preoperatively for pancreatic adenocarcinoma. J Gastrointest Oncol. 2015;6(4):343–57.
33. Bockhorn M, Uzunoglu FG, Adham M, Imrie C, Milicevic M, Sandberg AA, et al. Borderline resectable pancreatic cancer: a consensus statement by the International Study Group



Chapter 3

Treatment strategies and clinical outcomes in consecutive patients with locally advanced pancreatic cancer: a multicenter prospective cohort

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ABSTRACT

Background

Since current studies on locally advanced pancreatic cancer (LAPC) mainly report from single, high-volume centers, it is unclear if outcomes can be translated to daily clinical practice. This study provides treatment strategies and clinical outcomes within a multicenter cohort of unselected patients with LAPC.

Methods

Consecutive patients with LAPC according to Dutch Pancreatic Cancer Group criteria, were prospectively included in 14 centers from April 2015 until December 2017. A centralized expert panel reviewed response according to RECIST v1.1 and potential surgical resectability. Primary outcome was median overall survival (mOS), stratified for primary treatment strategy.

Results

Overall, 422 patients were included, of whom 77% (n=326) received chemotherapy. The majority started with FOLFIRINOX (77%, 252/326) with a median of six cycles (IQR 4-10). Gemcitabine monotherapy was given to 13% (41/326) of patients and nab-paclitaxel/gemcitabine to 10% (33/326), with a median of two (IQR 3-5) and three (IQR 3-5) cycles respectively. The mOS of the entire cohort was 10 months (95%CI 9-11). In patients treated with FOLFIRINOX, gemcitabine monotherapy, or nab-paclitaxel/gemcitabine, mOS was 14 (95%CI 13-15), 9 (95%CI 8-10), and 9 months (95%CI 8-10), respectively. A resection was performed in 13% (32/252) of patients after FOLFIRINOX, resulting in a mOS of 23 months (95%CI 12-34).

Conclusion

This multicenter unselected cohort of patients with LAPC resulted in a 14 month mOS and a 13% resection rate after FOLFIRINOX. These data put previous results in perspective, enable us to inform patients with more accurate survival numbers and will support decision-making in clinical practice.

INTRODUCTION

Pancreatic cancer is known for its limited treatment options and its poor overall survival.[1] Approximately 30-40% of patients present with locally advanced, unresectable pancreatic cancer (LAPC) due to extensive perivascular tumor infiltration without distant metastases.[1] Upfront surgery is generally deemed not beneficial for these patients. Therefore, treatment strategies for LAPC have been extrapolated from studies in patients with metastatic disease.[2,3] In recent years, the interest in treatment strategies aiming for local disease control[4,5] or disease regression with the potential for resection has rapidly increased.[6-8] Cohort studies report a median overall survival of 24 months in patients with LAPC treated with FOLFIRINOX (a combination of 5-fluorouracil, oxaliplatin, irinotecan and leucovorin).[7] Moreover, high-volume expert centers report resection rates of approximately 28% after FOLFIRINOX, with a very promising median overall survival (mOS) up to 35 months.[6,8,9] These studies, however are subject to referral bias and inclusion criteria of oncological trials are often limited to patients with favorable performance status, carrying the risk of sampling bias.[10,11] The external validity of these results for the overall population of patients with newly diagnosed LAPC is uncertain so that translation of these promising results into daily clinical practice is unclear.
Within the Netherlands, nationwide centralization of pancreatic cancer surgery was introduced in 2006.[12] As a result, patients with pancreatic cancer are routinely discussed at multidisciplinary tumor board (MDT) meetings within one of the pancreatic centers. In 2015, the prospective LAPC registry started including all consecutive patients presenting with LAPC. The aim of this multicenter prospective study is to give an overview of treatment strategies and clinical outcomes within a cohort of unselected patients with LAPC that reflects current clinical practice.

MATERIALS AND METHODS

Study population

Consecutive patients with suspected LAPC, based on imaging, were prospectively registered in 14 Dutch pancreatic centers from April 2015 until December 2017. Patients were identified at MDT meetings and LAPC was defined according to the Dutch Pancreatic Cancer Group (DPCG) criteria (Supplementary file 1).[13] Patients diagnosed with LAPC during upfront explorative laparotomy with the intention for resection were also eligible for study inclusion. Exclusion criteria were distant metastases, age <18 years or no informed consent. Distant lymph nodes were defined according to the consensus statement by the International Study Group of Pancreatic Surgery (ISGPS)[14] and considered as metastatic disease if pathologically proven. The study was performed according to the declaration of Helsinki. Written informed consent was obtained from

all patients and the ethical review boards approved the registry within all participating hospitals. To ensure external validity, the proportion of all patients with LAPC that were included in the cohort was determined by a crosscheck with the Dutch Cancer Registry, in which all patients are registered based on the International Classification of Diseases for Oncology (ICD-O-3).

Treatment strategies

The decision to start treatment was based on the advice of the multidisciplinary team meeting and shared decision-making with a medical oncologist. Typically, this advice consisted of treatment with FOLFIRINOX for Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0-1 patients, nab-paclitaxel/gemcitabine for ECOG PS 0-2 patients, and gemcitabine monotherapy for ECOG PS 2 patients. All patients treated with chemotherapy were restaged after four cycles of FOLFIRINOX or two cycles of gemcitabine (± nab-paclitaxel) with a thoracic and abdominal computed tomography (CT) according to a standardized biphasic contrast-enhanced protocol. Restaging CTs of LAPC patients were prospectively reviewed by a centralized nationwide expert panel consisting of abdominal radiologists, pancreatic surgeons, and interventional radiologists. The radiologist evaluated RECIST version 1.1 response and vascular involvement of the celiac trunk, superior mesenteric artery, hepatic artery and portomesenteric veins[15]. When there was no progression of disease, potential surgical resectability and eligibility for clinical trials was evaluated by pancreatic surgeons and interventional radiologists. An explorative laparotomy with intent for resection was advised in case of non-progressive and National Comprehensive Cancer Network (NCCN) borderline resectable disease (*i.e.* up to 180° arterial tumor abutment and reconstructable venous involvement or possibility for a modified Appleby resection).[16,17] In case of progression of disease, it was advised to stop chemotherapy. In case of stable disease or disease response without potential resectable disease, it was advised to continue chemotherapy or to include patient in a clinical trial. The expert panel advice was sent back to the treating medical oncologist by the study coordinator.

A new treatment episode was defined when a different treatment strategy was started, or when chemotherapy was re-introduced after progression of disease during a disease free period. Adjuvant chemotherapy after surgery or after ablative therapy was not scored as separate treatment episode. Discontinuation of chemotherapy and follow-up was based on local expertise. Typically, chemotherapy was stopped at progression of disease, intolerable toxicity or at patient's request. Depending on performance status and the treating medical oncologist, patients with progressive disease were offered second-line chemotherapy, included in clinical trials or treated with best supportive care. No (local) protocols were at hand for second-line chemotherapy during the study inclusion period.

Data collection and outcomes

Data on demographics, tumor characteristics, treatment strategies, and clinical outcomes were extracted from medical records. Missing data from patients that were (partially) treated in referring centers were retrieved. All baseline CTs were re-evaluated by experienced abdominal radiologists for vascular involvement. Primary outcome was overall survival. Secondary outcomes were treatment strategies, progression free survival, RECIST response at restaging, adverse events, resection rate after induction chemotherapy and postoperative outcomes. Overall survival was measured from date of diagnosis (*i.e.,* pathological proof or diagnosis at CT if no pathology was available) to date of death. Patients still alive at follow-up were censored. Progression was defined according to RECIST version 1.1 criteria, established on imaging or diagnosed during explorative laparotomy or diagnostic laparoscopy, or occurrence of death (all causes). Median overall and progression free survival were calculated as intention-to-treat analysis based upon the initial treatment strategy. Adverse events during chemotherapy treatment were graded according to the National Cancer Institute Common Terminology Criteria for Adverse (CTCAE) version 4.0.[18] Postoperative complications were defined according to the Clavien-Dindo classification and if occurring within 30 days or during the initial admission.[19] A radical resection margin (R0) was defined, according to the Royal College of Pathologists definition.[20]

Statistics

Statistical analyses were performed using IBM SPSS Statistics for Windows version 25.0 (IBM Corp., Orchard Road Armonk, New York, US). Data are presented as mean ± standard deviation (SD), or median with interquartile range (IQR) for continuous data and counts with percentage for categorical data. Treatment strategies were visualized in a Sankey diagram using SankeyMATIC (www.sankeymatic.com). Survival analyses were performed using the Kaplan–Meier method. To ensure comparability with published data, sensitivity analyses for overall survival and resection rate were performed for patients with NCCN locally advanced unresectable disease, since these are the reference standard in most studies.[16] In addition sensitivity analysis for resection rate was done for patients registered in the top three registering hospitals versus other hospitals to investigate effect of hospital volume. The chi-square test was used to compare resection rate between groups.

RESULTS

Within the study period, 422 patients were included from 14 centers. Baseline characteristics are given in Table 1. A small group of patients (n=14, 3%) was diagnosed

with LAPC during explorative laparotomy for presumed (borderline) resectable disease. After crosschecking a sample of n=205 patients registered as LAPC within the Dutch Cancer Registry within the same period, 85% (n=175) were registered in the cohort and another 8% (n=16) were captured but not eligible for inclusion. In total, 7% (n=14) of the sample of patients with LAPC registered within the Dutch Cancer Registry was not identified by the study team with unknown reasons.

Treatment strategies

Overall, 21% (n=87) of patients received no specific oncological treatment. About half of these patients (46/87, 53%) had a ECOG PS 0-1, but refused chemotherapy. Two percent (n=9) of patients received upfront treatment strategies other than chemotherapy. Of the remaining 77% (n=326) of patients who started chemotherapy, the majority primarily received FOLFIRINOX (252/326, 77%) with a median of six cycles (IQR 4-10). Nab-paclitaxel/gemcitabine was administered as first-line treatment to 10% of patients (33/326) with a median of two cycles (IQR 2-5), and 13% (41/326) of patients starting chemotherapy received gemcitabine monotherapy with a median of three cycles (IQR 2-5). Characteristics of patients stratified for primary treatment are given in Table 1. Patients treated with FOLFIRINOX were significantly younger, had a lower Charlson comorbidity Index, ECOG PS and CA19-9 and a higher albumin level at diagnosis when compared to other groups (Table 1).

Figure 1 gives an overview of all different treatment strategies for all patients. Overall, 79% (n=335) started anti-tumor treatment and 43% (n=183) of patients received a secondary treatment. 8% (n=32) received a resection, 10% (n=42) second line chemotherapy and 22% (n=91) local ablative therapy as secondary treatment. This consisted of stereotactic body radiation therapy (SBRT) (45/91, 49%), radiofrequency ablation (24/91, 26%), or irreversible electroporation (IRE) (22/91, 24%), mainly within clinical trials (61/91, 67%). Overall, 14% (n=58) underwent any tertiary anti-tumor treatment, and 4% (n=16) a fourth or a fifth treatment strategy.

Restaging and RECIST response

Of all patients who received chemotherapy as primary treatment, 13% (n=43) stopped treatment prematurely, due to toxicity (6%, n=19), on patients' request (4%, n=12), early progression (3%, n=11), or for unknown reason (0·3%, n=1). Of the remaining patients, 77% (219/283) was evaluated within the centralized expert panel, and 22% (63/283) within the treating hospitals after a median of eight weeks (IQR 7-10). One patient was lost to follow-up. Non-progressive disease at restaging was evaluated in respectively 193 (77%), 24 (73%), and 24 (59%) of all patients who started with FOLFIRINOX, nab-paclitaxel/gemcitabine and gemcitabine monotherapy. Response to chemotherapy is shown in Table 2.

Table 1. Patients baseline characteristics grouped by primary treatment

	All patients n=422	FOLFIRINOX n=252	Nab-paclitaxel/ gemcitabine n=33	Gemcitabine n=41	Best supportive care n=87	p -value
Age, years (SD)	66 (9)	63 (9)	70 (8)	71 (7)	71 (9)	**<0.001**
Male sex, n (%)	218 (52)	130 (52)	21 (64)	17 (42)	48 (55)	0.27
BMI (SD)[a]	23.9 (3.8)	24.2 (3.8)	24.2 (4.6)	23.6 (3.8)	23.0 (3.4)	0.07
CCI (IQR)	1 (0-2)	0 (0-1)	1 (0-3)	1 (0-2)	1 (0-2)	**0.001**
ECOG PS, n (%)[b]						**<0.001**
0	146 (35)	116 (46)	6 (18)	6 (15)	15 (17)	
1	167 (40)	101 (40)	17 (52)	18 (44)	28 (32)	
2	52 (12)	14 (6)	8 (24)	10 (24)	20 (23)	
3	14 (3)	2 (1)	1 (3)	3 (7)	8 (9)	
Biliary drainage, n (%)	218 (52)	122 (48)	17 (52)	23 (56)	52 (60)	0.30
Pain at baseline, n (%)[c]	320 (76)	195 (77)	27 (82)	25 (61)	65 (75)	0.22
CA19-9, kU/l (IQR)[d]	300 (52-1288)	274 (37-1200)	301 (32-725)	1046 (164-2620)	299 (52-1547)	**0.01**
Albumin, g/l (IQR)[e]	39 (34-42)	40 (35-43)	39 (33-42)	37 (33-42)	38 (34-41)	**0.01**
Tumor location, n (%)						0.35
Pancreatic head	285 (68)	168 (67)	25 (76)	25 (61)	64 (74)	
Pancreatic body and tail	137 (32)	84 (33)	8 (24)	16 (39)	23 (26)	
Tumor diameter, mm (IQR)[f]	40 (30-49)	40 (30-47)	37 (27-50)	40 (31-52)	38 (30-50)	0.67
Pathological proven adenocarcinoma, n (%)	390 (92)	240 (95)	32 (97)	39 (95)	71 (82)	**<0.001**

[a] *n*=24 missings; [b] *n*=43 missings; [c] any numeric rating scale pain score >0; *n*=14 missings; [d] *n*=98 missings; [e] *n*=110 missings; [f] for 12 patients tumor diameter was not measurable; Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; ECOG PS, Eastern Cooperative Oncology Group Performance Status

Overall and progression free survival

After a median follow-up of 9 months (IQR 5–15), 79% (335/422) of the patients had died. mOS of all patients was 10 months (95% CI 9–11). Patients not fit for chemotherapy and receiving best supportive care had a mOS of 3 months (95%CI 2–4), compared with 6 months (95%CI 5-7) for those who denied chemotherapy. Patients treated with FOLFIRINOX had a mOS of 14 months (95%CI 13-15), while patients receiving nab-paclitaxel/gemcitabine or gemcitabine monotherapy both had a mOS of 9 months (95%CI 8-10)(Table 2, Figure 2). Sensitivity analyses for patients with NCCN unresectable disease at diagnosis (n=326) showed similar results (best supportive care mOS 4 months (95%CI 3–5); FOLFIRINOX mOS 14 months (95%CI 12–16); nab-paclitaxel/gemcitabine mOS 9 months (95%CI 7–11); gemcitabine monotherapy mOS 9 months (95%CI 6–12)).

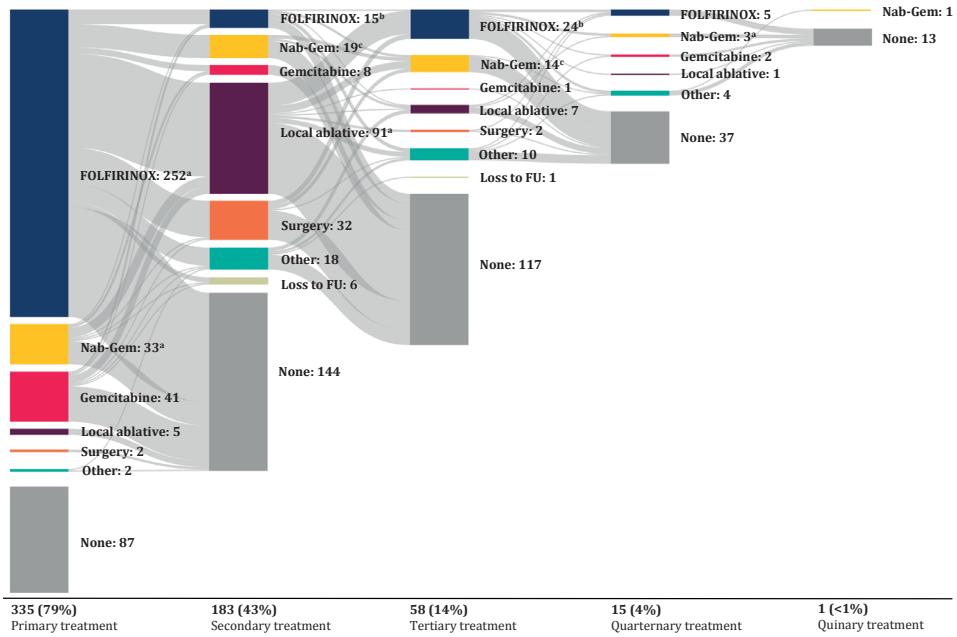


Figure 1. Sankey diagram of consecutive anti-tumor treatment strategies for all patients with LAPC
Made with http://www.sankeymatic.com. The colored blocks indicate different treatment strategies and a grey line represents a single patient or group of patients starting a new treatment episode. [a] The treatment of one patient was ongoing at the end of follow-up; [b] The treatment of four patients was ongoing at the end of follow-up; [c] The treatment of two patients was ongoing at the end of follow-up; Local ablative therapies include radiofrequency ablation (PELICAN trial), irreversible electroporation (PANFIRE, CROSSFIRE, IMPALA or ANTILOPE trial), and stereotactic body radiation (CROSSFIRE, LAPC-1 or SBRT trial). Other includes capecitabine (±gemcitabine), S-1, hyperthermia (±chemotherapy), immunotherapy (ALPS trial), docetaxel (CRITAX trial), sunitinib (SUNRISE trial), nab-paclitaxel + LDE225 (MATRIX trial) . Surgery indicates resected patients. Abbreviations: Gem, gemcitabine; Nab-Gem, nab-paclitaxel/gemcitabine; FU, follow-up.

In total, 254 (60%) patients showed either local progression of disease (n=67, 16%) and/or distant metastases (n=187, 44%) during follow-up. For patients treated with FOLFIRINOX, nab-paclitaxel/gemcitabine and gemcitabine monotherapy, median progression free survival was 8 months (95%CI 7-9), 7 months (95%CI 5-9), and 4 months (95%CI 3-5), respectively (Table 2).

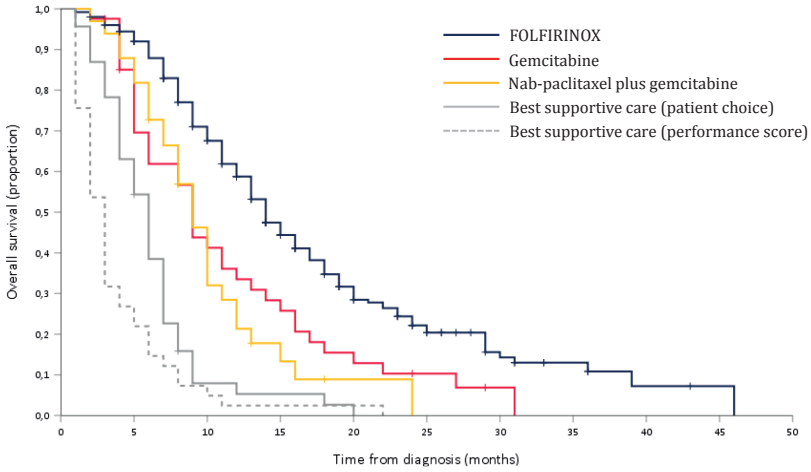
Adverse events during primary treatment

Fatal adverse events during chemotherapy treatment with FOLFIRINOX, nab-paclitaxel/gemcitabine and gemcitabine monotherapy were reported in respectively 2% (n=6), 0%, and 5% (n=2) of patients. Two patients treated with FOLFIRINOX died from a sepsis with neutropenia. Other fatal adverse events included a gastric hemorrhage (n=1), sepsis without neutropenia (n=1), cardiac arrest (n=1), and a bowel perforation (n=1). For patients treated with gemcitabine, adverse events leading to death were a cardiac arrest (n=1), and an ischemic cerebrovascular event (n=1). Most common grade 3 or 4

Table 2. Clinical outcomes for patients starting chemotherapy treatment

	FOLFIRINOX n=252	Nab-paclitaxel/ gemcitabine n=33	Gemcitabine n=41
Stop of treatment before restaging, n(%)	31 (12)	6 (18)	6 (15)
Toxicity	14 (6)	3 (9)	2 (5)
Patient request	7 (3)	2 (6)	3 (7)
Early progression on imaging	6 (2)	-	-
Clinical progression or death	3 (1)	1 (3)	1 (2)
Unknown	1 (<1)	-	-
RECIST response at restaging, n(%)[a,b]			
Partial response	33 (13)	1 (3)	1 (2)
Stable disease	160 (63)	23 (70)	23 (56)
Progressive disease	28 (11)	2 (6)	11 (27)
CA19-9 at restaging, kU/l (IQR)[c]	110 (29-585)	26 (5-182)	186 (69-444)
Overall survival, months (95%CI)	14 (13-15)	9 (8-10)	9 (8-10)
Progression free survival, months (IQR)	8 (7-9)	7 (5-9)	4 (3-5)
Resection rate, n(%)	32 (13)	1 (3)	1 (2)
R0 resection, n(% of resections)	17 (53)	0 (0)	0 (0)
Overall survival, months (95%CI)	23 (13-33)	5	16

[a] one patient treated with nab-paclitaxel/gemcitabine was lost to follow-up; [b] seven (nab-paclitaxel/) gemcitabine patients were restaged after three cycles. 16 FOLFIRINOX patients were restaged after 3, 5 or 6 cycles and 5 after a combination of 1-2 cycles FOLFIRINOX + 1-3 cycles (nab-paclitaxel/) gemcitabine. All other patients (*n*=254) were restaged after four cycles of FOLFIRINOX or two of (nab-paclitaxel/) gemcitabine; [c] CA19-9 at restaging was available for 113, 6 and 11 patients treated with FOLFIRINOX, nab-paclitaxel/gemcitabine and gemcitabine respectively; Abbreviations: RECIST, response evaluation criteria in solid tumors



Number at risk (number censored)										
FOLFIRINOX	252 (0)	233 (5)	164 (18)	93 (37)	49 (53)	25 (63)	12 (70)	6 (74)	2 (76)	1 (77)
Nab-paclitaxel /gemcitabine	33 (0)	29 (0)	13 (3)	4 (4)	1 (5)	0 (5)	0 (5)	0 (5)	0 (5)	0 (5)
Gemcitabine	41 (0)	33 (2)	17 (2)	11 (2)	6 (2)	3 (3)	1 (5)	0 (5)	0 (5)	0 (5)
Best supportive care (patient choice)	46 (0)	29 (0)	3 (2)	2 (2)	1 (2)	0 (2)	0 (2)	0 (2)	0 (2)	0 (2)
Best supportive care (performance score)	41 (0)	11 (0)	3 (0)	1 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Figure 2. Overall survival
Patients are grouped based upon primary treatment.

adverse events are summarized in Table 3. Neutropenia occurred in 33% (n=83), 30% (n=10), and 24% (n=10) of patients treated with FOLFIRINOX, nab-paclitaxel/gemcitabine and gemcitabine monotherapy, respectively. The most frequent non hematologic adverse event was diarrhea, occurring in 16% (n=40), 6% (n=2), and 2% (n=1) of patients treated with FOLFIRINOX, nab-paclitaxel/gemcitabine, and gemcitabine monotherapy, respectively.

Resection and postoperative outcomes

After induction chemotherapy, resection rate was 10% (34/326): 13% (32/252) for patients receiving FOLFIRINOX, 3% (1/33) within those receiving nab-paclitaxel/gemcitabine, and 2% (1/41) for gemcitabine monotherapy (Table 2). The majority of patients received FOLFIRINOX before surgical exploration (32/34, 94%), with a median of four cycles (IQR 4-8). In total, 44% (15/34) had a partial response at restaging and 56% (19/34) had stable disease. Sensitivity analysis for only those patients with NCCN unresectable disease at baseline showed a similar resection rate after induction chemotherapy: 8% (20/253, p=0·19). Sensitivity analysis for patients from the top three registering hospitals versus others showed a resection rate of 12% (23/200) versus 9% (11/126)(p=0·54).

Table 3. Most common grade 3 or 4 adverse occurring during primary chemotherapy

Event	FOLFIRINOX n=252	Nab-paclitaxel/ gemcitabine n=33	Gemcitabine n=41
Hematologic , n(%)[a]			
Neutropenia	83 (33)	10 (30)	10 (24)
Febrile neutropenia	17 (7)	4 (12)	-
Trombocytopenia	6 (2)	3 (9)	1 (2)
Anemia	4 (2)	4 (12)	2 (5)
Nonhematologic, n(%)[a]			
Diarrhea	40 (16)	2 (6)	1 (2)
Vomiting	21 (8)	2 (6)	-
Cholangitis	21 (8)	1 (3)	2 (5)
Thromboembolism	17 (7)	2 (6)	1 (2)
Fatigue	5 (2)	-	-
Sensory neuropathy	4 (2)	-	-
Elevated liver enzymes	4 (2)	2 (6)	-

[a] In *n*=4, *n*=1, and *n*=1 patients treated with FOLFIRINOX, nab-paclitaxel/gemcitabine, and gemcitabine, respectively, adverse events were missing.

A Clavien-Dindo ≥III complication occurred in 18/34 resected patients (53%). No patient died during the initial admission or within 30 days. The R0 resection rate was 50% (n=17). In total, 59% (20/34) of patients started adjuvant chemotherapy, mostly consisting of FOLFIRINOX (85%, 17/20). During follow-up, 56% (19/34) of patients developed disease recurrence, of whom six had R0 resection, and 13 R1 resection. Median disease-free survival after surgery was 9 months (95%CI 4–14). The mOS for all patients who underwent a resection was 23 months (95%CI 12–34) from diagnosis (Table 2).

DISCUSSION

This multicenter prospective cohort of consecutive patients with LAPC reflecting real-world data demonstrated a mOS of 10 months for all patients. Chemotherapy was administered to 77% of patients in the entire cohort. The majority received FOLFIRINOX demonstrating a mOS of 14 months. In patients treated with nab-paclitaxel/gemcitabine or gemcitabine monotherapy mOS was 9 months. After a median of four cycles FOLFIRINOX, 13% underwent a resection reporting a mOS of 23 months.

Overall survival in patients with LAPC treated with gemcitabine monotherapy ranges from 10 to 12 months in published trials.[21,22] There have been several treatment developments afterwards. With the introduction of FOLFIRINOX[2], a patient level meta-analysis in patients with LAPC reported an improved overall survival of 24 months for patients receiving FOLFIRINOX as primary treatment.[7] Results for nab-paclitaxel/gemcitabine within patients with LAPC are scarce, but the regimen showed a two months survival benefit when compared to gemcitabine monotherapy in patients with metastatic disease.[23] When compared to the current cohort, especially a 14 months overall survival in consecutive patients treated with FOLFIRINOX is substantially lower than the aforementioned results reported from literature. This difference can be explained by referral bias and confounding by indication in published series from single, highly experienced centers, and emphasizes the relevance of reporting unselected results. This hypothesis is substantiated by a recent study including consecutive patients with borderline resectable and locally advanced pancreatic cancer resulting in a 13 months overall survival for all patients, comparable to this cohort.[24] When considering nab-paclitaxel/gemcitabine, care must be taken when interpreting these data, since results might be immature due to small patient numbers. Within the Netherlands, nab-paclitaxel/gemcitabine was registered as a treatment for pancreatic cancer from July 2015. Thereafter it was implemented within standard of care, mostly for WHO 1-2 patients, during this study. This explains low patient numbers and worse outcomes when compared to published series. A phase II trial from Japan started in July 2016 and randomizes patients with LAPC between modified FOLFIRINOX and nab-paclitaxel/gemcitabine with 1-year overall survival as primary endpoint. This study will provide important data on clinical relevant endpoints of this relatively new treatment regimen.[25]

Since the introduction of FOLFIRINOX, an increasing number of cohort studies demonstrated encouraging results for patients undergoing a resection after chemotherapy with a median overall survival ranging from 22 to 35 months and a resection rate of 28%.[6,8,9,26] In the current cohort, a median overall survival of 23 months in the selection of patients undergoing a resection is in line with previous published studies, while a 13% resection rate in consecutive patients treated with FOLFIRINOX is lower than previously reported. In addition to the earlier mentioned risk of biases, differences in selecting patients eligible for explorative laparotomy might have contributed to this discrepancy. In the current study, patient selection was based solely upon radiology criteria, while others advocate to select on the basis of CA19-9 or even explore all patients with RECIST stable disease.[8,27] In addition, few centers would even consider performing arterial resection and reconstruction in LAPC patients, while this is currently not done within the Netherlands.[28] Although survival after resection is promising, the actual survival benefit of resection of LAPC is unclear since these patients

are by definition those with favorable prognostic characteristics. Ideally, future studies should match patients with and without resection based upon age, performance status and response to chemotherapy, including CA19-9 among other possible predictors, to enhance insight in this important clinical question.

The variety of multimodal treatment strategies within this cohort shows the current lack of treatment paradigm for LAPC after first-line treatment. Questions remain regarding the timing and role of second- or third-line therapies after FOLFIRINOX as first-line treatment, as well as which patients to select. CT cannot accurately evaluate response to chemotherapy[27] and methods such as more accurate imaging modalities and (personalized) biomarkers are needed.[29,30] Several ablative and systemic therapies are now under investigation in randomized clinical trials. Initiated in the Netherlands and now also in other European countries, the ongoing multicenter PELICAN RCT (clinicaltrails.gov; NCT03690323) aims to assess the added value of radiofrequency ablation over standard palliative chemotherapy. The Dutch multicenter CROSSFIRE trial compares FOLFIRINOX plus MR-guided SBRT to FOLFIRINOX plus percutaneous IRE (clinicaltrials.gov NCT02791503). Another multicenter randomized trial from the United States investigates modified FOLFIRINOX ± SBRT (registered at clinicaltrials.gov NCT01926197). Pending these results, ablative strategies in LAPC should not be considered as standard treatment due to the lack of randomized data.

This study has some limitations. First, a crosscheck of patients with the Dutch Cancer Registry showed that, although including consecutive patients, a proportion of 7% of the LAPC population was not identified by the study team. These were mainly older patients treated with best supportive care and not always presented at the MDT meeting. This might have overestimated the proportion of patients eligible for anti-cancer treatment and overall survival of the total cohort. This bias is inevitable and most studies do not have insight in these numbers. Second, some patients were included after radiological imaging only, which might have introduced some misdiagnosed patients within the cohort. This, however, comprised only 8% of patients and was necessary to gather outcomes on patients treated only with best supportive care. Third, the DPCG definition for LAPC[13] was used. These criteria differ from the NCCN criteria, which are considered as the reference standard by many authors.[16] However, sensitivity analysis did not show difference between patients with NCCN or DPCG unresectable disease, suggesting a minimum impact of this variation in definition.

The strengths of this study include the multicenter design including all patients with LAPC from a large group of centers with a predefined follow-up. The difference in outcomes compared to literature emphasizes the relevance of reporting multicenter

patient population based cohort data of consecutive patients with LAPC. Within the study, there was no difference in resection rate between low and high volume hospitals. A centralized expert panel evaluating all patients is likely to have contributed to comparable treatment strategies and ensured a structured RECIST assessment and standardized advice concerning resectability and trial inclusion. Furthermore, patient inclusion will be continued for the coming years to enlarge patient numbers and enable future research focusing on prediction models, quality of life and selecting patients for resection and ablative therapy, among others.

In conclusion, the current study is the first to present an unselected multicenter prospective cohort of consecutive patients with LAPC and showed a median overall survival of 10 months in all patients, 14 months after FOLFIRINOX and 9 months after (nab-paclitaxel/)gemcitabine treatment. Selected patients, eligible for a resection after neoadjuvant chemotherapy showed a median overall survival of 23 months. The present study presents data representative for current clinical practice within the Netherlands, and enable us to inform patients with realistic survival data, supporting decision-making in daily clinical practice.

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REFERENCES

1. Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. *Lancet* 2011;378(9791):607e20. https://doi.org/10.1016/S0140-6736(10)62307-0.
2. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364(19):1817e25. https://doi.org/10.1056/NEJMoa1011923.
3. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369(18):1691e703. https://doi.org/10.1056/NEJMoa1304369.
4. Rombouts SJE, Vogel JA, Van Santvoort HC, et al. Systematic review of innovative ablative therapies for the treatment of locally advanced pancreatic cancer. Br J Surg 2015;102(3):182e93. https://doi.org/10.1002/bjs.9716.
5. Vogel JA, Rombouts SJ, de Rooij T, et al. Induction chemotherapy followed by resection or irreversible electroporation in locally advanced pancreatic cancer (IMPALA): a prospective cohort study. Ann Surg Oncol 2017;24(9):2734e43. https://doi.org/10.1245/s10434-017-5900-9.
6. Rombouts SJ, Walma MS, Vogel JA, et al. Systematic review of resection rates and clinical outcomes after FOLFIRINOX-based treatment in patients with locally advanced pancreatic cancer. Ann Surg Oncol 2016;23(13):4352e60. https://doi.org/10.1245/s10434-016-5373-2.
7. Suker M, Beumer BR, Sadot E, et al. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. Lancet Oncol 2016;17(6):801e10. https://doi.org/10.1016/S1470-2045(16)00172-8.
8. Hackert T, Sachsenmaier M, Hinz U, et al. Locally advanced pancreatic cancer:neoadjuvant therapy with folfirinox results in resectability in 60% of the patients. Ann Surg 2016;264(3):457e61. https://doi.org/10.1097/SLA.0000000000001850.
9. Gemenetzis G, Groot VP, Blair AB, et al. Survival in locally advanced pancreatic cancer after neoadjuvant therapy and surgical resection. Ann Surg 2019. https://doi.org/10.1097/SLA.0000000000002753. epublished.
10. David JM, Kim S, Placencio-Hickok VR, Torosian A, Hendifar A, Tuli R. Treatment strategies and clinical outcomes of locally advanced pancreatic cancer patients treated at high-volume facilities and academic centers. Adv Radiat Oncol 2019;4(2):302e13. https://doi.org/10.1016/j.adro.2018.10.006.
11. Amini A, Jones BL, Stumpf P, et al. Patterns of care for locally advanced pancreatic adenocarcinoma using the national cancer database. Pancreas 2017;46(7):904e12. https://doi.org/10.1097/MPA.0000000000000876.
12. De Wilde RF, Besselink MGH, Van Der Tweel I, et al. Impact of nationwide centralization of pancreaticoduodenectomy on hospital mortality. Br J Surg 2012;99(3):404e10. https://doi.org/10.1002/bjs.8664.
13. Dutch Pancreatic Cancer Group. Definitions of resectability pancreatic cancer. Published, http://www.dpcg.nl/richtlijnen-classificaties/dpcg-definities.html. [Accessed 13 March 2019].
14. Tol JAMG, Gouma DJ, Bassi C, et al. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the International Study Group on Pancreatic Surgery (ISGPS). Surgery 2014;156(3):591e600. https://doi.org/10.1016/j.surg.2014.06.016.
15. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Canc 2009;45(2):228e47. https://doi.org/10.1016/j.ejca.2008.10.026.
16. Herman J, Ko AH, Komanduri S, et al. Pancreatic adenocarcinoma, version 2.2017 clinical practice guidelines in Oncology NCCN categories of evidence and consensus. JNCCN-Journal Natl Compr Cancer Netw 2017;15(8):1028e61. https://doi.org/10.6004/jnccn.2017.0131.
17. Klompmaker S, Boggi U, Hackert T, et al. Distal pancreatectomy with celiac Axis resection (DP-CAR) for pancreatic cancer. How I do it. J Gastrointest Surg 2018;22(10):1804e10. https://doi.org/10.1007/s11605-018-3894-7.
18. National Cancer Institute. Common Terminology criteria for adverse events v4.0. 2010. Published, https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. [Accessed 1 April 2015].
19. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240(2):205e13. https://doi.org/10.1097/01.sla.0000133083.54934.
20. The Royal College of Pathologists. Dataset for the histopathological reporting of pancreatic, ampulla of Vater and bile duct carcinoma 2017. 2017. Published, www.rcpath.org. [Accessed 1 May 2019].
21. Louvet C, Labianca R, Hammel P, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. J Clin Oncol 2005;23(15):3509e16. https://doi.org/10.1200/JCO.2005.06.023.

22. Lima CMR, Green MR, Rotche R, et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. J Clin Oncol 2004;22(18):3776e83. https://doi.org/10.1200/JCO.2004.12.082.
23. Von Hoff DD, Goldstein D, Renschler MF, et al. Albumin-bound paclitaxel plus gemcitabine in pancreatic cancer. N Engl J Med 2014;370(5):478. https://doi.org/10.1056/NEJMc1314761.
24. Maggino L, Malleo G, Marchegiani G, et al. Outcomes of primary chemotherapy for borderline resectable and locally advanced pancreatic ductal adenocarcinoma. JAMA Surg 2019;154(10):932e42. https://doi.org/10.1001/jamasurg.2019.2277.
25. Mizusawa J, Fukutomi A, Katayama H, et al. Protocol digest of randomized phase II study of modified FOLFIRINOX versus gemcitabine plus nab-paclitaxel combination therapy for locally advanced pancreatic cancer: Japan clinical oncology group study (JCOG1407). Pancreatology; 2018. https://doi.org/10.1016/j.pan.2018.07.007. Published online.
26. Rangelova E, Wefer A, Persson S, et al. Surgery improves survival after neoadjuvant therapy for borderline and locally advanced pancreatic cancer. Ann Surg 2019:1. https://doi.org/10.1097/SLA.0000000000003301. Published online.
27. Ferrone CR, Marchegiani G, Hong TS, et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. Ann Surg 2015;261(1):12e7. https://doi.org/10.1097/SLA.0000000000000867.
28. Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years after. Surgery 2017;161(3):584e91. https://doi.org/10.1016/j.surg.2016.11.014.
29. Cassinotto C, Sa-Cunha A, Trillaud H. Radiological evaluation of response to neoadjuvant treatment in pancreatic cancer. Diagn Interv Imaging 2016;97(12):1225e32. https://doi.org/10.1016/j.diii.2016.07.011.
30. Cheng SH, Cheng YJ, Jin ZY, Xue HD. Unresectable pancreatic ductal adenocarcinoma: role of CT quantitative imaging biomarkers for predicting outcomes of patients treated with chemotherapy. Eur J Radiol 2019;113:188e97. https://doi.org/10.1016/j.ejrad.2019.02.009.

SUPPLEMENTARY MATERIAL

Supplementary file 1. Dutch Pancreatic Cancer Group criteria of resectability at diagnosis, based on computed tomography imaging (2012)

	SMA	Celiac axis	CHA	SMV-PV
Resectable (all required)	No contact	No contact	No contact	≤90° contact
Borderline resectable (minimally one required)	≤90° contact	≤90° contact	≤90° contact	90° - ≤270° contact, no occlusion
Locally advanced (minimally one required)	>90° contact	>90° contact	>90° contact	>270° contact, or occlusion

Abbreviations: SMA, superior mesenteric artery; CHA, common hepatic artery; SMV, superior mesenteric vein; PV, portal vein.

Chapter 4

The treatment and survival of elderly patients with locally advanced pancreatic cancer: post-hoc analysis in a multicenter registry

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ABSTRACT

Background

The treatment options for patients with locally advanced pancreatic cancer (LAPC) have improved in recent years and consequently survival has increased. It is unknown, however, if elderly patients benefit from these improvements in therapy. With the ongoing aging of the patient population and an increasing incidence of pancreatic cancer, this patient group becomes more relevant. This study aims to clarify the association between increasing age, treatment and overall survival in patients with LAPC.

Methods

Post-hoc analysis of a multicenter registry including consecutive patients with LAPC, who were registered in 14 centers of the Dutch Pancreatic Cancer Group (April 2015-December 2017). Patients were divided in three groups according to age (<65, 65-74 and ≥75 years). Primary outcome was overall survival stratified by primary treatment strategy. Multivariable regression analyses were performed to adjust for possible confounders.

Results

Overall, 422 patients with LAPC were included; 162 patients (38%) aged <65 years, 182 patients (43%) aged 65-74 and 78 patients (19%) aged ≥75 years. Chemotherapy was administered in 86%, 81% and 50% of the patients in the different age groups ($p<0.01$). Median overall survival was 12, 11 and 7 months for the different age groups ($p<0.01$). Patients treated with chemotherapy showed comparable median overall survival of 13, 14 and 10 months for the different age groups ($p=0.11$). When adjusted for confounders, age was not associated with overall survival.

Conclusion

Elderly patients are less likely to be treated with chemotherapy, but when treated with chemotherapy, their survival is comparable to younger patients.

INTRODUCTION

In the Netherlands, overall survival of pancreatic cancer has hardly improved in the last decades.[1] It is predicted that pancreatic cancer will be the second most common cause of cancer related death in 2030.[2] At presentation, only 10–20% of the patients are eligible for surgery and 30–35% of the patients are diagnosed with locally advanced pancreatic cancer (LAPC).[3-5] The current standard first line treatment for patients with LAPC is chemotherapy.[6] The most frequently used regimens of chemotherapy are a (modified) combination of 5-fluorouracil, oxaliplatin, irinotecan and leucovorin (FOLFIRINOX), nab-paclitaxel plus gemcitabine (NABGEM), and gemcitabine monotherapy. FOLFIRINOX and NABGEM have shown their benefit in randomized trials in patients with metastatic disease.[7,8] Although no randomized trials have been reported for LAPC, several cohort studies suggested a survival benefit for these regimens as well.[9-11] The use of (chemo) radiation in LAPC is still controversial. Studies suggests that (chemo)radiation is safe and feasible, however, survival benefit has not yet been proven.[5,9,13]

With the aging population and the increasing incidence of pancreatic cancer, advanced age in patients with pancreatic cancer becomes more relevant.[14] Limited data suggests that elderly patients with pancreatic cancer also benefit from chemotherapy.[15,16] Although an increased incidence of adverse events is seen, toxicity of the chemotherapeutic regimens seems to be acceptable in this patient group.[17,18] This, however, does not always translate to similar treatment strategies in the daily clinical practice.[15,16] Elderly patients are rarely included in clinical trials and are more often treated with best supportive care.[15,19,20] Moreover, elderly patients with pancreatic cancer are reported to have a worse prognosis in general.[21] It remains unclear, whether this worse prognosis is truly age dependent or due to retraining treatment, since data in the elderly patient population are scarce.

The present study aims to clarify the association between increasing age, primary treatment strategies and overall survival. A large unselected cohort of patients with LAPC representing daily clinical care for pancreatic cancer in the Netherlands was analyzed.

METHODS

Study design and population

This is a post-hoc analysis of a multicenter registry including consecutive patients with LAPC, diagnosed between April 2015 and December 2017, in 14 centers collaborating in the Dutch Pancreatic Cancer Group.

All patients aged >18 years, diagnosed with LAPC were included. This diagnosis was based on radiologic examination or findings during upfront explorative laparotomy, according to the Dutch Pancreatic Cancer Group criteria (Supplementary Table S1). All patients gave informed consent for registration and the Institutional Review Boards approved the registry within all participating centers. We adhered to the STROBE guidelines.[22]

Data collection

Patient demographics, tumor characteristics, serum CA 19.9, treatment modalities, adverse events according to Common Terminology Criteria for Adverse Events version 4.0[23] and survival were extracted from the retrospective database. For best supportive care, the registration included the reason why best supportive care was chosen (patient's choice or condition). Survival was measured from date of diagnosis (i.e. pathological proof or CT at diagnosis if no pathologic proof was available) to date of death from all causes. Patients still alive at follow-up were censored. Patients were divided in three age groups; <65 years, 65–74 years and ≥75 years; aiming for equal and clinically relevant proportions between the groups.[15,24,25] According to the World Health Organization (WHO) criteria patients aged over 65 years are defined as elderly.[26] This study defined the patients aged over 75 years as the true elderly.

Statistical analyses

Descriptive statistics were performed with IBM SPSS Statistics for Windows version 25.0 (IBM Corp., Orchard Road Armonk, New York, US). Data are presented as mean ± standard deviation (SD), or median with interquartile range (IQR) when appropriate for continuous data and counts with percentage for categorical data. Differences in baseline characteristics were tested using Chi-square or Fisher exact test and continuous variables were compared using the One way ANOVA or Kruskal-Wallis H test. Overall survival was estimated with Kaplan Meier curves. Multivariable logistic regression was performed to assess the influence of age on the start of treatment with chemotherapy. Possible confounders that were corrected for included sex, World Health Organization performance score (WHO performance score), Charlson Comorbidity Index (CCI score), tumor size, tumor location, and baseline serum CA 19.9. Results are given as odds ratios (OR) with 95% confidence interval (CI). Multivariate Cox regression analysis was performed to assess the influence of age on overall survival. Possible confounders that were corrected for included sex, WHO performance score, CCI score, tumor size, tumor location, baseline serum CA 19.9 and treatment strategy. Results are given as hazard ratios (HR) with 95% CI. A sensitivity analysis was performed by excluding all patients with WHO performance score 2–3. A p-value <0.05 was considered statistically significant.

RESULTS

Patient and tumor characteristics

Overall, 422 patients diagnosed with LAPC met our eligibility criteria, 162 patients (38%) aged <65 years, 182 patients (43%) aged 65–74 years and 78 patients (19%) aged ≥75 years. Patient and tumor characteristics are summarized in Table 1. The median age at diagnosis was 68 years (range 25–92). Patients had overall good clinical performance scores (WHO performance score 0–1 in 89%, 80% and 73% of patients aged <65, 65–74 and ≥75 years, respectively, p<0.01). Comorbidities were different between the age groups (median CCI score of 0, 1 and 1 in the three age groups, p<0.01). An increased age resulted in less often obtained pathological diagnosis (97%, 91% and 86% in patients aged <65, 65–74 and ≥75 years, respectively, p<0.01). The tumor location and tumor size were comparable between groups, with most tumors located in the pancreatic head.

Table 1. Patient and tumor characteristics in three age groups of patients with locally advanced pancreatic cancer

	All patients n=422	Age<65 n=162	Age 65-74 n=182	Age≥75 n=78	p -value
Age, median [range]	68 [25-92]	58 [25-64]	70 [65-74]	78 [75-92]	
Gender, n(%)					0.58
Male	218 (52)	79 (49)	99 (54)	40 (51)	
Female	204 (48)	83 (51)	83 (46)	38 (49)	
CCI score, median [IQR][a]	1 [0-2]	0 [0-1]	1 [0-2]	1 [0-2]	**<0.01**
WHO PS, n (%)[b]					**<0.01**
0-1	313 (83)	133 (89)	131 (80)	49 (73)	
≥1	66 (17)	16 (11)	32 (20)	18 (27)	
Pathologic confirmation, n (%)					**<0.01**
Yes	390 (92)	157 (97)	166 (91)	67 (86)	
No	32 (8)	5 (3)	16 (9)	11 (14)	
Tumor location, n (%)					0.12
Pancreatic head	285 (68)	103 (64)	122 (67)	60 (77)	
Pancreatic body/tail	137 (32)	59 (36)	60 (33)	18 (23)	
Tumor size, mm, median [IQR][c]	41 [30-49]	42 [31-50]	40 [30-47]	40 [28-46]	0.49
CA19-9, median [IQR][d]	300 [52-1288]	228 [40-1243]	330 [99-1669]	173 [27-586]	**0.04**

[a]1 missing; [b]43 missing; [c]12 missing; [d]98 missing. Abbreviations: CCI, Charlston Comorbidity Index; WHO PS, World Health Organization performance score; CA 19.9, carbohydrate antigen 19.9.

Treatment strategy

Treatment modalities per age group are presented in Table 2. The primary treatment modality differed between the age groups (p<0.01). The majority of the patients aged <65 years and 65–74 years were treated with chemotherapy, as compared to only half of the patients aged ≥75 years (86%, 81% and 50% in patients aged <65, 65–75 and ≥75 years). Best supportive care was administered most often in the elderly patients (12%, 18% and 46% in patients aged <65 years, 65–74 years and ≥75 years, respectively, p<0.01). Reasons to chose for best supportive care were similar between age groups. Approximately half of the patients actively chose this approach, whereas the other half of the patients were treated with best supportive care because of a poor clinical condition. Chemotherapeutic regimens differed between the age groups (p<0.01). In patients aged <65 and 65–74 years FOLFIRINOX was the most frequently administered chemotherapy (in 78% and 63%, respectively), whereas in the patients aged ≥75 years Nab-paclitaxel plus gemcitabine or gemcitabine monotherapy were administered more often (both in 18% of the patients aged ≥75 years). Comparable results were seen in a sensitivity analysis for patients with WHO performance score 0–1, who were treated with chemotherapy or best supportive care. The proportion of patients with WHO performance score 0–1 that was treated with chemotherapy differed with age (in the three age groups: 90%, 88%, and 60%, p<0.01). Of the patients aged ≥75 years, with WHO performance score 0–1 who were treated with chemotherapy, FOLFIRINOX was given in the minority (22%).

Table 2. First-line treatment strategies in three age groups of patients with locally advanced pancreatic cancer

	All patients n=422	Age<65 n=162	Age 65-74 n=182	Age≥75 n=78	p-value
Best supportive care, n (%)	87 (21)	19 (12)	32 (18)	36 (46)	<0.01
Chemotherapy, n (%)					
FOLFIRINOX	252 (60)	126 (78)	115 (63)	11 (14)	
NABGEM	33 (8)	8 (5)	11 (6)	14 (18)	
Gemcitabine	41 (10)	5 (3)	22 (12)	14 (18)	
Other, n (%)	9 (2)	4 (2)	2 (1)	3 (4)	

NABGEM, Nab-paclitaxel plus gemcitabine.

Grade 3 and higher adverse events associated with chemotherapy treatment occurred more often in younger patients (66% of patients aged <65 years, 61% of patients aged 65–74 years, and 34% of patients aged ≥75 years, p<0.01). Overall, the most common hematologic adverse event that occurred was neutropenia (32%). Furthermore, febrile

Table 3. Adverse events grade 3 and 4 during chemotherapy, per age group

	Age<65 n=139	Age 65-74 n=148	Age≥75 n=39	p-value
Hematologic, n (%)[a]				
Neutropenia	41 (30)	52 (35)	10 (26)	0.43
Febrile neutropenia	9 (7)	9 (6)	3 (8)	0.90
Thrombocytopenia	4 (3)	4 (3)	2 (5)	0.67
Anemia	4 (3)	3 (2)	3 (8)	0.14
Nonhematologic. n (%)[a]				
Diarrhea	19 (14)	21 (14)	3 (8)	0.64
Vomiting	10 (7)	12 (8)	1 (3)	0.56
Thromboembolism	12 (9)	5 (3)	3 (8)	0.13
Fatigue	5 (4)	0 (0)	0 (0)	0.05
Sensory neuropathy	3 (2)	1 (1)	0 (0)	0.61
Elevated liver enzymes	2 (1)	3 (2)	1 (3)	0.85

[a] 6 missing.

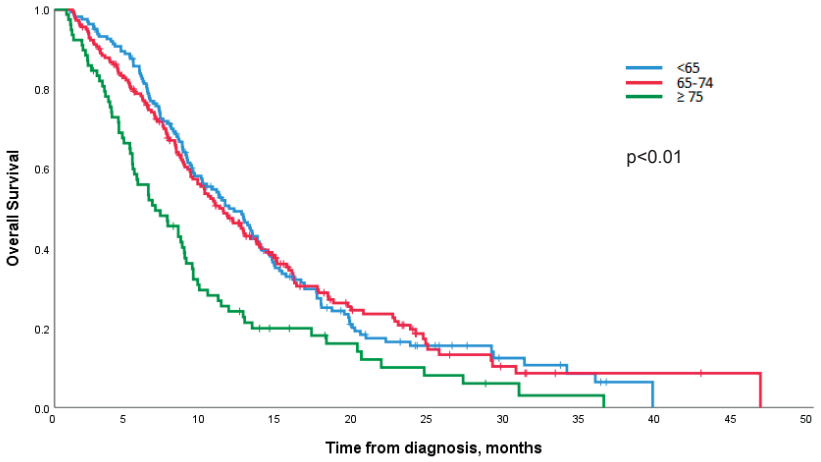
neutropenia (6%), thrombocytopenia (3%), and anemia (3%) were reported. Non-hematologic adverse events that occurred often were diarrhea (13%), vomiting (7%), and thromboembolism (6%). The occurring of the most common adverse events in the different age groups is presented in Table 3 (all not significantly different).

A multivariable analysis on the influence of age on the probability for treatment with chemotherapy, adjusted for confounders, showed that each additional year in age was associated with a decreased probability to receive chemotherapy (OR 0.94, 95% CI 0.89–0.98, p=0.01).

Survival

In all age groups, patients treated with chemotherapy had longer median overall survival, as compared with patients treated with best supportive care (13 vs 6 months in patients <65 year, p<0.01; 14 vs 3 months in patients 65–74 year, p<0.01; and 10 vs 4 months in patients ≥75 year, p<0.01). Kaplan Meier survival curves are shown in Figure 1, Figure 2. Patients aged ≥75 years had a lower median overall survival, compared to the younger patients groups (12 months in patients aged <65 years, 11 months in patients aged 65–74 years, and 7 months in patients aged ≥75 years, p<0.01). Survival did not differ significantly in patients treated with chemotherapy (in the three age groups: 13, 14, and 10 months, p=0.11). In patients treated with FOLFIRINOX chemotherapy median overall survival did not differ significantly as well (in the three age groups: 13, 15, and 20 months, p=0.23).

A multivariate Cox regression analysis on the influence of age on overall survival, adjusted for confounders, showed that an increase in age was not associated with a decrease in overall survival (HR 0.99, 95% CI 0.98–1.02, p=0.83).



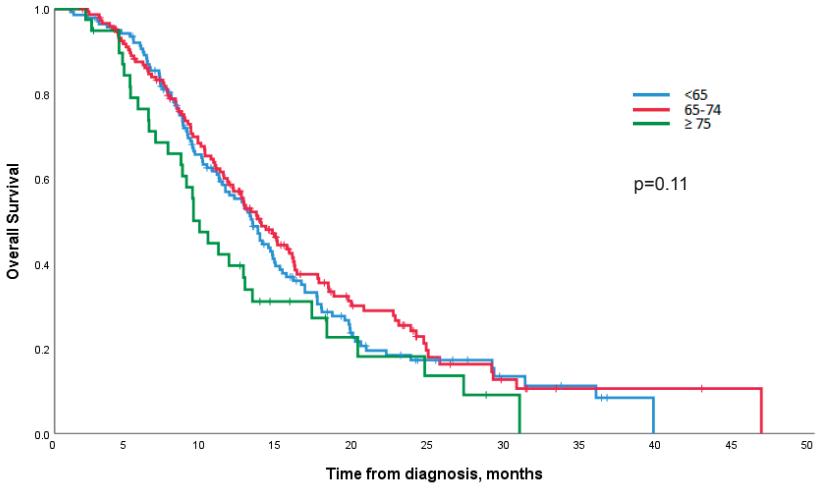
Number at risk (number censored)											
Patients <65	162 (0)	144 (1)	87 (9)	49 (15)	24 (21)	14 (25)	7 (30)	4 (31)	0 (33)	0 (33)	0 (33)
Patients 65-74	182 (0)	147 (5)	92 (14)	52 (25)	28 (34)	12 (41)	6 (43)	2 (46)	2 (46)	1 (47)	0 (47)
Patients ≥75	78 (0)	52 (1)	23 (2)	12 (5)	8 (7)	4 (7)	2 (8)	1 (8)	0 (8)	0 (8)	0 (8)

Figure 1. Kaplan Meier Survival curve for overall survival in all patients with locally advanced pancreatic cancer, aged <65 years, 65-74 years, and ≥75 years, regardless of treatment

DISCUSSION

This multicenter cohort study aimed to clarify the association between increasing age, primary treatment strategies, and survival outcomes in consecutive patients with LAPC. Patients aged ≥75 years, with a good clinical condition, were less likely to be treated with chemotherapy. While treatment with chemotherapy showed an improvement in survival in elderly patients, similar to younger patients. Age was not independently associated with a decreased survival.

The increasing life expectancy of the general population results in an increasing number of elderly patients with LAPC.[27] The importance and need to offer a meaningful treatment to this group is therefore increasingly relevant. With new chemotherapeutic regimens, the treatment options for patients with pancreatic cancer have improved.[7,8] Since elderly patients are underrepresented in most clinical studies, it is uncertain to



Number at risk (number censored)											
Patients <65	139 (0)	130 (1)	84 (9)	47 (15)	23 (21)	13 (25)	6 (30)	4 (31)	0 (33)	0 (33)	0 (33)
Patients 65-74	148 (0)	132 (5)	91 (13)	52 (24)	28 (33)	12 (40)	6 (42)	2 (45)	2 (45)	1 (46)	0 (46)
Patients ≥75	39 (0)	33 (1)	19 (1)	9 (4)	5 (6)	3 (6)	1 (7)	0 (7)	0 (7)	0 (7)	0 (7)

Figure 2. Kaplan Meier survival curve for overall survival in patients with locally advanced pancreatic cancer, aged <65 years, 65–74 years, and ≥75 years, who were treated with chemotherapy

which extent they benefit from these treatment regimens.[28-30] More data on the risks and benefit of chemotherapy will improve the complex process of shared decision-making in elderly patients with LAPC. In recent studies, the focus on elderly patients increased, suggesting that they might benefit from treatment with chemotherapy, even when receiving modified regimens.[15,16,24,31] Consistent with our findings, median overall survival up to 12 months in elderly patients (aged ≥70 years) treated with chemotherapy is described in previous studies.[16,32-34] More important, in our study, patients aged ≥75 years, who were treated with FOLFIRINOX, had a median overall survival up to 20 months. Although this group only consisted of 11 patients (with age 75–80 years, WHO performance score 0–1, and CCI score 0–2), these results suggest that highly selected, fit, elderly patients should be considered for treatment with FOLFIRINOX chemotherapy as well.

Even though more information about chemotherapy in elderly patients is becoming available, the risk and impact of toxicity in this patient group is still unclear. An increased number of adverse events is seen in elderly patients treated with chemotherapy, nevertheless toxicity is found acceptable in most studies.[17,18,34] In our study, the overall rate of adverse events was less in patients aged ≥75 years, as compared to younger

patients. The occurrence of hematologic and nonhematologic adverse events did not differ in the age groups. This might be due to the administration of gemcitabine with or without Nab-paclitaxel more often in this already selected patient group, since these chemotherapeutic regimens are less toxic compared to FOLFIRINOX.[7] It might also suggest that the toxicity of chemotherapy in elderly patients is acceptable.

It has been suggested that age itself is not a negative prognostic factor for survival.[35,36] The performance score and comorbidity (CCI score) are proven prognostic factors. [37-40] Age itself decreases the probability of receiving treatment, as seen in our results as well.[19,41,42] Literature reported that approximately half of the elderly patients are treated with chemotherapy, which is in line with our results.[19,20] Furthermore, we observed that about half of the patients treated with best supportive care specifically chose this treatment strategy over chemotherapy. Unfortunately, we do not know which factors contributed to this shared decision-making process. In previous studies, it was observed that elderly patients are not always properly informed of their diagnosis and sometimes they are treated according to their physicians or family's preferences.[15,43] In our cohort, all patients gave informed consent to participate in this study, so it is unlikely that they were not informed about their diagnosis and treatment options.

This study has several limitations. First, information about frailty in the elderly patients is lacking. Although this study reports about the clinical condition of all patients, due to the retrospective nature of this study frailty scores are not available. The Comprehensive Geriatric Assessment (CGA) is shown effective in geriatric oncology by identifying vulnerable elderly and optimizing cancer and overall treatment and should be recommended to use in the decision-making process.[44] Second, there might be referral bias. All included patients were presented at the multidisciplinary team meeting in the referral hospitals. There is a possibility that some patients, especially those with a poor performance status or high age, were not referred to the participating expert pancreatic centers and could therefore not be included. Third, our true elderly population consists of patients aged 75 years and older. Currently, there is no consensus on who are the real elderly patients and different age thresholds are suggested in literature. Some studies use the definition of octogenarians (≥80 years) to describe elderly patients. In our cohort, however, there were too few patients aged ≥80 years (n=19) for a valid analysis. Fourth, due to the retrospective nature of this study, there are missing data. Although we know if patients were treated with best supportive care due to a poor condition or by choice, we do not know the exact considerations leading to this decision.

In conclusion, in this multicenter LAPC cohort selected elderly patients, who are treated with chemotherapy, have similar survival as younger patients. Therefore, chemotherapy should probably be considered more often in fit elderly patients and be taken in account in the process of shared decision-making.

AUTHORS CONTRIBUTION

Study concepts and design: LJHB, MSW, HCvS, MGB, IQM.
Data acquisition: all authors.
Statistical analysis, data analysis and interpretation: LJHB, MSW.
Manuscript preparation: LJHB.
Manuscript editing and review: all authors.
Final approval of the manuscript: all authors.

DECLARATION OF COMPETING INTEREST

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REFERENCES

1. Latenstein AEJ, van der Geest LGM, Bonsing BA, et al. Nationwide trends in incidence, treatment and survival of pancreatic ductal adenocarcinoma. Eur J Canc 2020;125:83e93.
2. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Canc Res 2014;74(11):2913e21.
3. Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. Lancet (London, England) 2011;378(9791):607e20.
4. Philip PA. Locally advanced pancreatic cancer: where should we go from here? J Clin Oncol : official journal of the American Society of Clinical Oncology 2011;29(31):4066e8.
5. Reames BN, Blair AB, Krell RW, et al. Management of locally advanced pancreatic cancer: results of an international survey of current practice. Ann Surg 2019. Epub ahead of print.
6. van Veldhuisen E, van den Oord C, Brada LJ, et al. Locally advanced pancreatic cancer: work-up, staging, and local intervention strategies. Cancers 2019;11(7).
7. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364(19):1817e25.
8. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369(18):1691e703.
9. Suker M, Beumer BR, Sadot E, et al. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. Lancet Oncol 2016;17(6):801e10.
10. Rombouts SJ, Walma MS, Vogel JA, et al. Systematic review of resection rates and clinical outcomes after FOLFIRINOX-based treatment in patients with locally advanced pancreatic cancer. Ann Surg Oncol 2016;23(13):4352e60.
11. Saito T, Ishido K, Kudo D, et al. Combination therapy with gemcitabine and nab-paclitaxel for locally advanced unresectable pancreatic cancer. Molecular and clinical oncology 2017;6(6):963e7.
12. Peterson SL, Husnain M, Pollack T, et al. Neoadjuvant nab-paclitaxel and gemcitabine in borderline resectable or locally advanced unresectable pancreatic adenocarcinoma in patients who are ineligible for FOLFIRINOX. Anticancer Res 2018;38(7):4035e9.
13. Suker M, Nuyttens JJ, Eskens FALM, et al. Efficacy and feasibility of stereotactic radiotherapy after folfirinox in patients with locally advanced pancreatic cancer (LAPC-1 trial). EClinicalMedicine 2019;17:100200.
14. Kontis V, Bennett JE, Mathers CD, Li G, Foreman K, Ezzati M. Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble. Lancet (London, England) 2017;389(10076):1323e35.
15. Kuroda T, Kumagi T, Yokota T, et al. Efficacy of chemotherapy in elderly patients with unresectable pancreatic cancer: a multicenter review of 895 patients. BMC Gastroenterol 2017;17(1):66.
16. Berger AK, Abel U, Komander C, Harig S, Jager D, Springfeld C. Chemotherapy for advanced pancreatic adenocarcinoma in elderly patients (>/¼70 years of age): a retrospective cohort study at the National Center for Tumor Diseases Heidelberg. Pancreatology : official journal of the International Association of Pancreatology (IAP) [et al] 2014;14(3):211e5.
17. Li X, Huang DB, Zhang Q, et al. The efficacy and toxicity of chemotherapy in the elderly with advanced pancreatic cancer. Pancreatology : official journal of the International Association of Pancreatology (IAP) [et al] 2020;20(1):95e100.
18. Mizrahi JD, Rogers JE, Hess KR, et al. Modified FOLFIRINOX in pancreatic cancer patients Age 75 or older. Pancreatology 2020;20(3):501e4.
19. Nipp R, Tramontano AC, Kong CY, et al. Disparities in cancer outcomes across age, sex, and race/ethnicity among patients with pancreatic cancer. Cancer medicine 2018;7(2):525e35.
20. Dale DC. Poor prognosis in elderly patients with cancer: the role of bias and undertreatment. J Support Oncol 2003;1(4 Suppl 2):11e7.
21. Amin S, Lucas AL, Frucht H. Evidence for treatment and survival disparities by age in pancreatic adenocarcinoma: a population-based analysis. Pancreas 2013;42(2):249e53.
22. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 2007;335(7624):806e8.

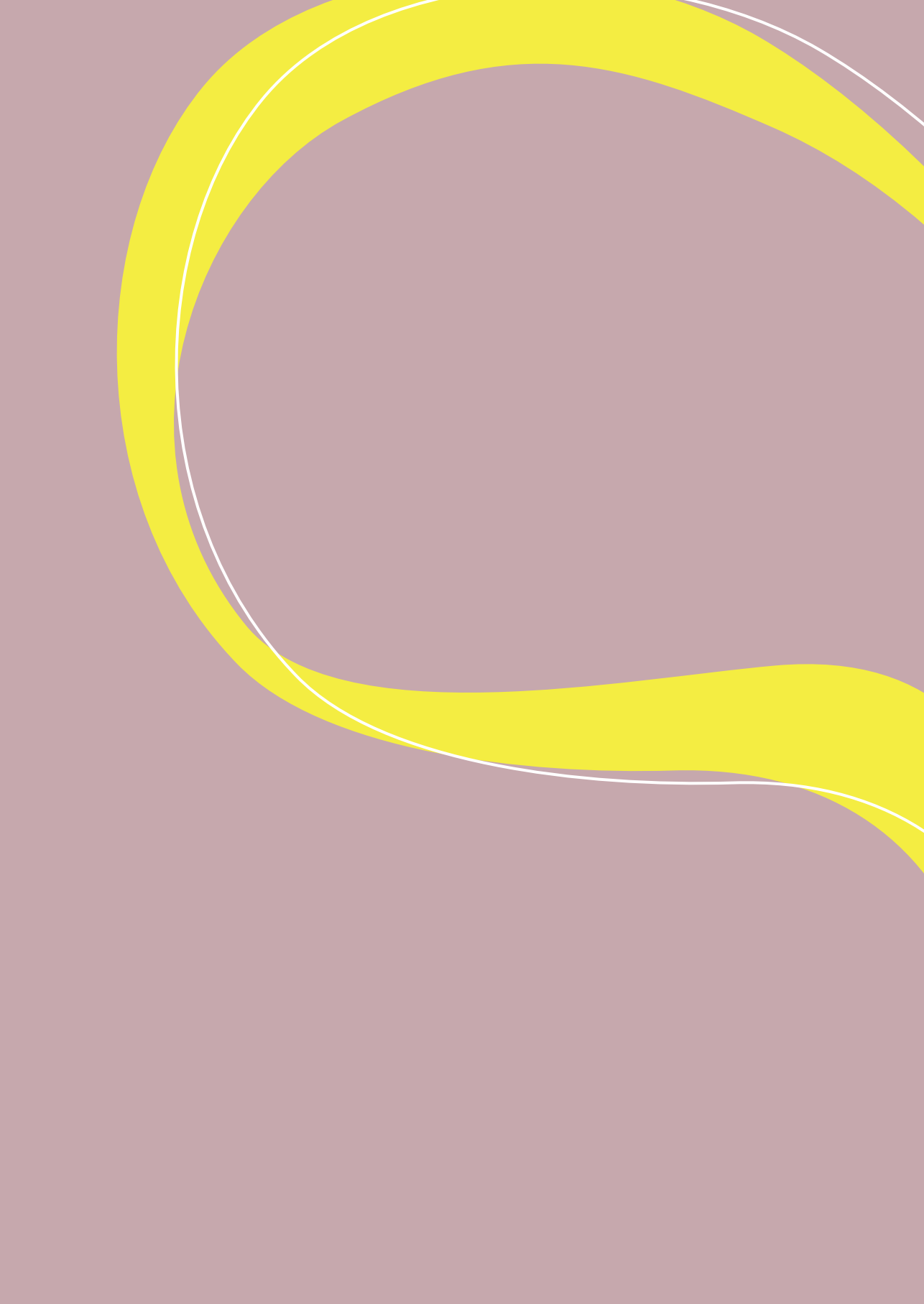
23. National Cancer Institute. Common Terminology criteria for adverse events v4.0. 2010. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. [Accessed 1 April 2015].
24. Macchini M, Chiaravalli M, Zanon S, et al. Chemotherapy in elderly patients with pancreatic cancer: efficacy, feasibility and future perspectives. Canc Treat Rev 2019;72:1e6.
25. van der Geest LGM, van Eijck CHJ, Groot Koerkamp B, et al. Trends in treatment and survival of patients with nonresected, nonmetastatic pancreatic cancer: a population-based study. Cancer medicine 2018;7(10):4943e51.
26. WHO, Geneva: Switzerland. World Health Organisation. Definition of an older or elderly person. http://www.who.int/healthinfo/survey/ageingdefnolder/en/index.html; 2010.
27. WHO. Global Health observatory data; life expectancy. Geneva: Switzerland: World Health Organization; 2019.
28. Hutchins LF, Unger JM, Crowley JJ, Coltman Jr CA, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med 1999;341(27):2061e7.
29. Lewis JH, Kilgore ML, Goldman DP, et al. Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol : official journal of the American Society of Clinical Oncology 2003;21(7):1383e9.
30. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. J Clin Oncol : official journal of the American Society of Clinical Oncology 2004;22(22):4626e31.
31. Tas F, Sen F, Keskin S, Kilic L, Yildiz I. Prognostic factors in metastatic pancreatic cancer: older patients are associated with reduced overall survival. Molecular and clinical oncology 2013;1(4):788e92.
32. Baldini C, Escande A, Bouche O, et al. Safety and efficacy of FOLFIRINOX in elderly patients with metastatic or locally advanced pancreatic adenocarcinoma: a retrospective analysis. Pancreatology : official journal of the International Association of Pancreatology (IAP) [et al] 2017;17(1):146e9.
33. Yamagishi Y, Higuchi H, Izumiya M, et al. Gemcitabine as first-line chemotherapy in elderly patients with unresectable pancreatic carcinoma. J Gastroenterol 2010;45(11):1146e54.
34. Guion-Dusserre JF, Bertaut A, Ghiringhelli F, et al. Folfirinox in elderly patients with pancreatic or colorectal cancer-tolerance and efficacy. World J Gastroenterol 2016;22(42):9378e86.
35. Castel-Kremer E, De Talhouet S, Charlois AL, et al. An onco-geriatric approach to select older patients for optimal treatments of pancreatic adenocarcinoma. Journal of geriatric oncology 2018;9(4):373e81.
36. Higuera O, Ghanem I, Nasimi R, Prieto I, Koren L, Feliu J. Management of pancreatic cancer in the elderly. World J Gastroenterol 2016;22(2):764e75.
37. Nakai Y, Isayama H, Sasaki T, et al. Comorbidity, not age, is prognostic in patients with advanced pancreatic cancer receiving gemcitabine-based chemotherapy. Crit Rev Oncol-Hematol 2011;78(3):252e9.
38. Kadokura M, Ishida Y, Tatsumi A, et al. Performance status and neutrophillymphocyte ratio are important prognostic factors in elderly patients with unresectable pancreatic cancer. J Gastrointest Oncol 2016;7(6):982e8.
39. Chen YG, Pan HH, Dai MS, et al. Impact of comorbidity and age on determinants therapeutic strategies in advanced pancreatic head cancer patients with obstructive jaundices. Medicine 2015;94(31):e1298.
40. Kougioumtzopoulou AS, Syrigos KN, Saif MW. Elderly patients with pancreatic cancer. JOP : J Pancreas 2014;15(4):322e5.
41. King JC, Zenati M, Steve J, et al. Deviations from expected treatment of pancreatic cancer in octogenarians: analysis of patient and surgeon factors. Ann Surg Oncol 2016;23(13):4149e55.
42. Shaib WL, Jones JS, Goodman M, et al. Evaluation of treatment patterns and survival outcomes in elderly pancreatic cancer patients: a surveillance, epidemiology, and end results-medicare analysis. Oncol 2018;23(6):704e11.
43. Oziel-Taieb S, Faure M, Gilabert M, et al. Treatment of pancreatic adenocarcinoma in elderly patients over 75 Years of age: a retrospective series of 129 patients. J Gastrointest Canc 2016;47(1):15e9.
44. Wildiers H, Heeren P, Puts M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol 2014;32(24):2595e603.
45. Orimo H, Ito H, Suzuki T, Araki A, Hosoi T, Sawabe M. Reviewing the definition of "elderly". Geriatr Gerontol Int 2006;6(3):149e58.

SUPPLEMENTARY MATERIAL

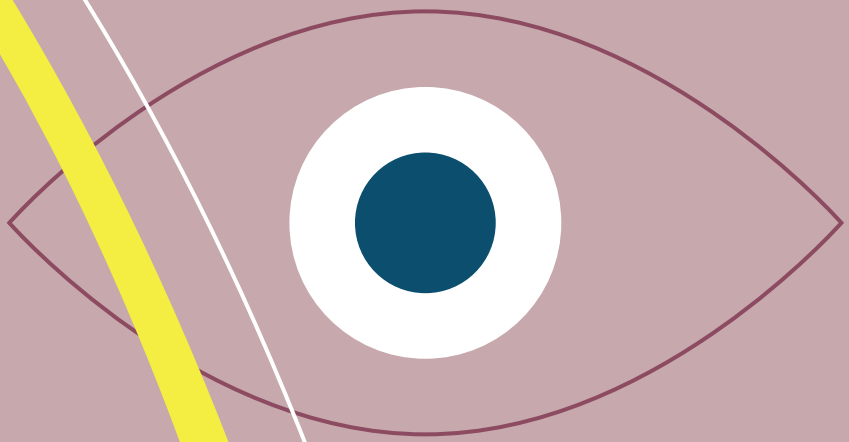
Table S1. Dutch Pancreatic Cancer Group criteria for locally advanced pancreatic cancer

	SMA	Celiac axis	CHA	SMV-PV
Locally advanced (minimally one required)	>90° contact	>90° contact	>90° contact	>270° contact, or occlusion

Abbreviations: SMA, superior mesenteric artery; CHA, common hepatic artery; SMV, superior mesenteric vein; PV, portal vein



PART II
Outcome prediction



Chapter 5

Predicting overall survival and resection in patients with locally advanced pancreatic cancer treated with FOLFIRINOX: development and internal validation of two nomograms

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ABSTRACT

Background

Patients with locally advanced pancreatic cancer (LAPC) are increasingly treated with FOLFIRINOX, resulting in improved survival and resection of tumors that were initially unresectable. It remains unclear, however, which specific patients benefit from FOLFIRINOX. Two nomograms were developed predicting overall survival (OS) and resection at the start of FOLFIRINOX chemotherapy for LAPC.

Methods

From our multicenter, prospective LAPC registry in 14 Dutch hospitals, LAPC patients, starting first-line FOLFIRINOX (April 2015-December 2017) were included. Stepwise backward selection according to the Akaike Information Criterion was used to identify independent baseline predictors for OS and resection. Two prognostic nomograms were generated.

Results

A total of 252 patients were included, with a median OS of 14 months. 32 patients (13%) underwent resection, with a median OS of 23 months. Older age, female sex, Charlson Comorbidity Index≤1 and CA 19.9≤274 were independent factors predicting a better OS (c-index: 0.61). WHO ps >1, involvement of the SMA, celiac trunk, and SMV≥270° were independent factors decreasing the probability of resection (c-index: 0.79).

Conclusion

Two nomograms were developed to predict OS and resection in patients with LAPC before starting treatment with FOLFIRINOX. These nomograms could be beneficial in the shared decision-making process and counseling of these patients.

INTRODUCTION

It is estimated, that 30-35% of patients who are diagnosed with pancreatic cancer have locally advanced disease (LAPC).[1,2] LAPC is characterized by extensive vascular involvement, which precludes surgical resection of the tumor.[3] Over the last decades, median overall survival (OS) in these patients remained only around 11 months.[4] With the introduction of newer chemotherapeutic regimens, such as FOLFIRINOX (a combination of leucovorin, 5-fluorouracil, plus irinotecan, and oxaliplatin), the OS of patients with LAPC improved, resulting in an OS of 15-24 months.[5-7] Nowadays, the majority of patients with LAPC is treated with first line FOLFIRINOX.[8] Optional modified dose-regimens of FOLFIRINOX are associated with acceptable toxicity.[9-10]

After induction chemotherapy, some patients in whom the tumor was initially determined unresectable can actually undergo tumor resection. In patients with LAPC, treated with FOLFIRINOX, resection rates ranging from 20-60% have been described.[5,6,11,12] Median OS in these patients is up to 35 months.[12,13]

It is not yet established, however, in which specific patients FOLFIRINOX chemotherapy increases survival and which patients will become eligible for tumor resection. Studies reporting these outcomes were mostly single center studies with a highly selected patient population, including many tertiary referrals. Prospective data from a large cohort reflecting a real world setting are therefore needed. These data can be used to design nomograms for OS and the probability of tumor resection. This could be of value during the individual shared decision-making process and guide treatment decisions on whether to start FOLFIRINOX treatment or not. Nomograms are commonly used in oncologic clinical practice for clinical decision-making and patient counseling.[14] We therefore sought to identify prognostic baseline factors from a nationwide prospective multicenter cohort of patients with LAPC who were treated with FOLFIRINOX. Two nomograms to predict OS and tumor resection were developed.

MATERIAL AND METHODS

Patient selection

This study was conducted as part of a prospective observational registry study, which included consecutive patients diagnosed with LAPC between April 2015 and December 2017 in 14 centers in the Netherlands, affiliated with the Dutch Pancreatic Cancer Group (DPCG).[15] LAPC was defined according to the DPCG criteria[16] and established on radiologic imaging or during upfront explorative laparotomy. For the current study, we

selected all patients who started first line treatment with FOLFIRINOX. Patients treated with other first line therapies, and patients treated with best supportive care were excluded. All patients gave informed consent for registration and the Institutional Review Boards approved the registry within all participating centers.

Data collection

We performed a literature search to identify potential prognostics baseline factors for OS and tumor resection in patients with ductal pancreatic adenocarcinoma. Based on this literature search the following variables were chosen: age, gender, World Health Organization performance score (WHO performance score), Charlson Comorbidity Index (CCI score), pain, jaundice, weight loss, tumor size, tumor location, TNM stage (8th AJCC edition[17]), baseline serum CA 19.9, and vascular involvement (based on radiologic imaging) of the superior mesenteric artery (SMA), common hepatic artery (CHA), celiac trunk, portal vein (PV), and superior mesenteric vein (SMV). Treatment variables collected were: the number of chemotherapy cycles given, surgical exploration with or without resection. Baseline CT-scans and evaluation CT-scans after induction chemotherapy (i.e. 4 cycles FOLFIRINOX) were prospectively evaluated by a national expert panel including experienced abdominal radiologists and pancreatic surgeons. The radiologists scored the vascular involvement and response according to RECIST version 1.1.[18] Pancreatic surgeons reviewed all tumors according to the National Comprehensive Cancer Network (NCCN) criteria[3], to assess whether resection after induction chemotherapy was possible. Based on this multidisciplinary expert panel the decision to proceed to surgery was made, taking the tumor response and relation to the venous and arterial vasculature as evaluated on imaging into account. Data from baseline CT-scans were used for the development of the models. OS was measured from date of LAPC diagnosis until date of death. Patients were censored if they were still alive at final follow-up.

Statistical analysis and model development

Continuous data were presented as median with interquartile range (IQR) and categorical data as counts with percentage. OS was estimated using the Kaplan Meier method and the log-rank test was used to analyze differences between groups. Missing data were handled by multiple imputation, to which 10 datasets were created. Each analysis was performed in 10 imputed datasets. Pooled estimates and statistics were reported.

The prognostic models were developed according to the PROBAST criteria and were reported according to the TRIPOD statement.[19,20] Multivariable regression analyses were performed to investigate independent prognostic factors for overall survival (Cox regression) and probability of resection (logistic regression). For both models, backward selection (LR) according to the Akaike Information Criterion was used for model development. The predictive accuracy of the models was assessed using the

concordance statistics (c-index) or receiver operating characteristic curve (ROC-curve). Calibration plots were developed for each model to compare the predicted outcomes with the actual outcomes. Bootstrapping with 500 resamples was used for internal validation of the models. After internal validation two nomograms were developed. Analyses were performed using IBM SPSS Statistics for Windows version 25.0 (IBM Corp., Orchard Road Armonk, New York, US) and R version 3.6.1 (The R Project for Statistical Computing, Vienna, Austria; cran.r-project.org). A two-sided p-value of less than 0.05 was considered statistically significant

RESULTS

Patient cohort

Figure 1 shows the flowchart of patient selection and treatment. Within the study period, a total 252 patients underwent first line treatment with FOLFIRINOX. Baseline characteristics are presented in Table 1. The mean age was 65 years (IQR 57-70 years) and approximately half of the patients were men (52%, 130/252). Most tumors were located in the pancreatic head (67%, 168/252), with a median tumor size of 40 mm. Patients undergoing resection seem to have a better WHO ps (WHO 0-1 in 100%, 30/30 vs 92%, 187/203), and smaller tumor size (35 vs 40mm).

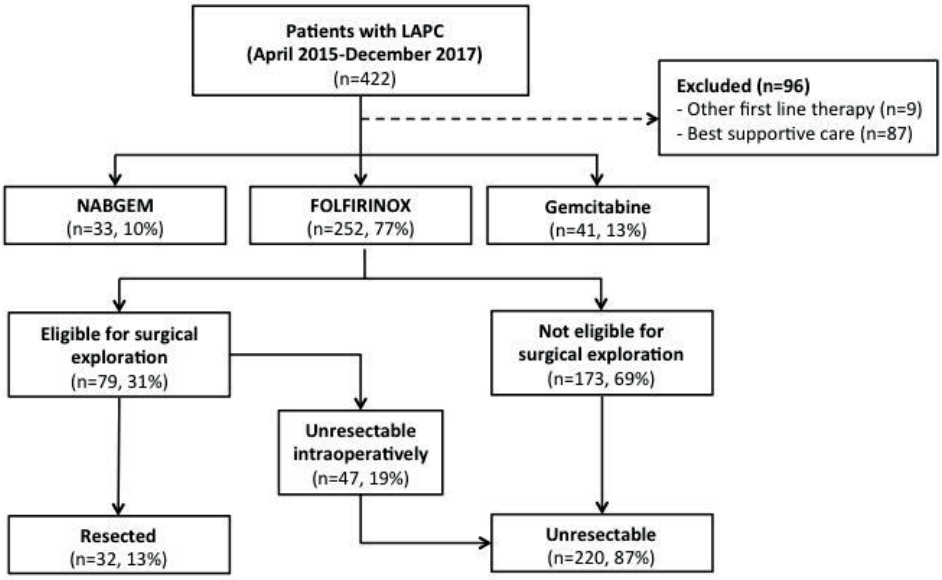


Figure 1. Flowchart of patient selection
NABGEM, nab-paclitaxel plus gemcitabine.

Table 1. Baseline patient and tumor characteristics

	All n=252	Non-resected patients n=220	Resected patients n=32
Age, median [IQR]	65 [57-70]	65 [57-70]	65 [60-71]
Sex, n (%)			
Male	130 (52)	112 (51)	18 (56)
Female	122 (48)	108 (49)	14 (44)
Weight loss, n (%)[a]			
Yes	200 (82)	177 (83)	23 (72)
No	44 (18)	35 (17)	9 (28)
Jaundice, n (%)[b]			
Yes	93 (37)	82 (37)	11 (35)
No	157 (63)	137 (63)	20 (65)
Pain, n (%)[c]			
Yes	195 (80)	171 (81)	24 (75)
No	48 (20)	40 (18)	8 (25)
Charlson Comorbidity Index, n (%)			
0-1	202 (80)	176 (80)	26 (81)
≥2	50 (20)	44 (20)	6 (19)
WHO ps, n (%)[d]			
0-1	217 (93)	187 (92)	30 (100)
≥2	16 (7)	16 (8)	0 (0)
Tumor location, n (%)			
Pancreatic head	168 (67)	143 (65)	25 (78)
Pancreatic body/tail	84 (33)	77 (35)	7 (22)
Tumor size, mm, median [IQR][e]	40 [30-47]	40 [30-49]	35 [27-44]
T stage, n (%)			
≤T3	73 (29)	55 (25)	18 (56)
T4	179 (71)	165 (75)	14 (44)
N stage, n (%)			
N0	182 (72)	161 (73)	21 (66)
N1	70 (28)	59 (27)	11 (34)
CA 19.9, median [IQR][f]	274 [37-1200]	274 [37-1243]	268 [33-790]
Cycles FOLFIRINOX, median [IQR][g]	6 [4-10]	7 [4-10]	4 [4-8]

[a]8 missing; [b]2 missing; [c]9 missing; [d]19 missing; [e]4 missing; [f]47 missing; [g] 2 missing; IQR, interquartile range; WHO ps, World Health Organization performance score; CA19.9, carbohydrate antigen 19.9.

After 4 cycles of induction FOLFIRINOX, 221 patients (88%, 221/252) underwent response evaluation via cross section imaging according to RECIST 1.1.[18] Progressive disease was seen in 28 patients (13%, 28/221), stable disease in 160 patients (72%, 160/221), and 33 patients (15%, 33/221) had a partial response. A total of 79 patients (31%, 79/252) underwent explorative laparotomy, of whom 32 patients (13%, 32/252) subsequently underwent tumor resection. Patients that could not undergo tumor resection continued

their chemotherapeutic regimen. Of the resected patients, 20 patients (63%, 20/32) received adjuvant chemotherapy, of whom 17 continued FOLFIRINOX. Postoperative outcomes of resected patients are presented in Supplemental Table 1.

Median OS in all 252 patients was 14.1 months (95% confidence interval (CI) 12.9-15.7 months). One- and 2-year survival was 59% and 22% respectively. Patients undergoing tumor resection had a median OS of 23.4 months (95% CI 13.9-32.9 months), as compared to 13.3 months (95% CI 12.1-14.6 months) in patients who did not undergo tumor resection (p<0.01). One- and 2-year survival in resected patients was 87% and 49% respectively. Survival curves are shown in Figure 2.

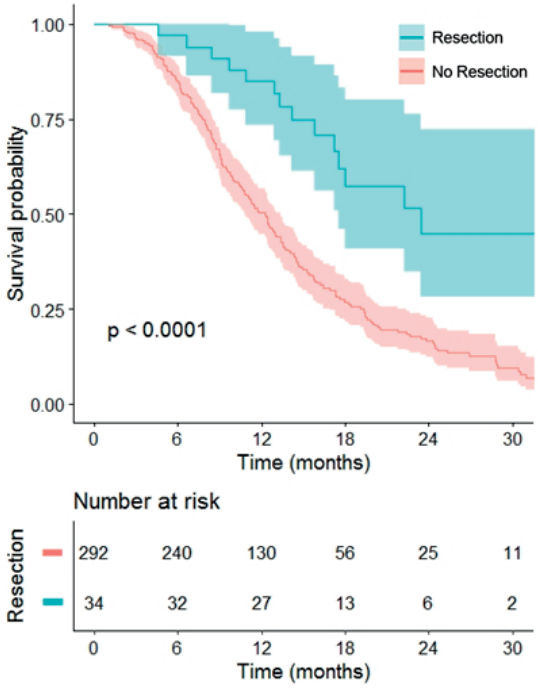


Figure 2. Comparison of overall survival (with corresponding 95% confidence intervals) between resected and unresected patients with locally advanced pancreatic cancer, all started treatment with FOLFIRINOX

Prognostic factors

The results for both prognostic models are given in Table 2. The model for OS included age, sex, CCI score and serum CA 19.9. The c-index of this model was 0.61, with a calibration slope of 0.98 for 1-year survival, and a calibration slope of 0.58 for 2-year survival (Supplemental Figure 1). Bootstrapping, with 500 resamples, yielded a c-index of 0.60.

Table 2a. Multivariable Cox regression analysis to predict overall survival in patients with locally advanced pancreatic cancer, who started first line treatment with FOLFIRINOX

	HR	95% CI	p-value
Age	0.97	[0.95-0.99]	<0.01
Sex (male vs female)	0.71	[0.53-0.97]	0.03
Charlson Comorbidity Index (≤1 vs >1)	2.01	[1.38-2.94]	<0.01
CA 19.9 (≤274 vs >274)	1.33	[0.97-1.82]	0.08

CA19.9, carbohydrate-antigen 19.9

Table 2b. Multivariable logistic regression analysis to predict the probability for resection in patients with locally advanced pancreatic cancer, who started treatment with first line FOLFIRINOX

	OR	95%CI	p-value
WHO ps (≤1 vs >1)	0.26	[0.03-1.11]	0.12
SMA			
<90°	Ref	-	-
90°-180°	0.23	[0.06-0.67]	0.01
≥180°	0.27	[0.06-0.85]	0.05
Celiac trunk			
<90°	Ref	-	-
90°-180°	0.38	[0.09-1.19]	0.13
≥180°	0.11	[0.01-0.52]	0.03
SMV (<270° vs ≥270°)	0.18	[0.04-0.57]	<0.01

WHO ps, World Health Organization performance score; SMA, superior mesenteric artery; SMV, superior mesenteric vein.

The model for resection included WHO performance score, and vascular involvement of the SMA, celiac trunk, and SMV. The c-index was 0.79, with a calibration slope of 1.02 (Supplemental Figure 2). The c-index after bootstrapping was 0.79.

Nomograms

The nomograms for both models are shown in Figure 3. With the first model (Figure 3a), the probability of 1-year survival between 20 and 80% can be predicted. The probability of 2-year survival can be predicted between 1 and 60%. The second model (Figure 3b) predicts the probability of a resection between 1 and 35%.

Both nomograms can be used for an individual patient according to the following steps: (1) determine the total points for each prognostic or predictive variable by drawing a straight line upwards from the variable point to the top point reference line, (2) sum the points for each variable, and (3) draw a straight line from the sum of the total points

on the reference line to the bottom probability lines to determine the patient's likelihood of 1- or 2-year survival or the likelihood of resection. Both prediction models are also available online via www.pancreascalculator.com.

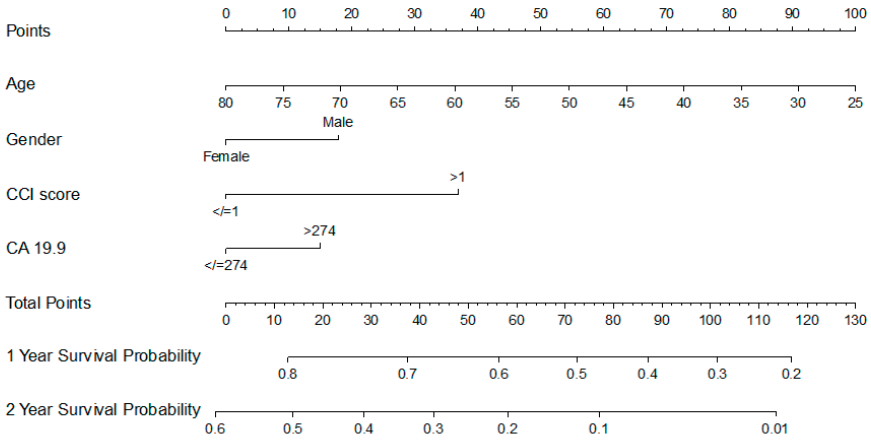


Figure 3a. Nomogram predicting 1- and 2-year survival in patients with locally advanced pancreatic cancer starting treatment with FOLFIRINOX
CCI score indicates Charlson Comorbidity Index, CA 19.9 indicates carbohydrate antigen 19.9.

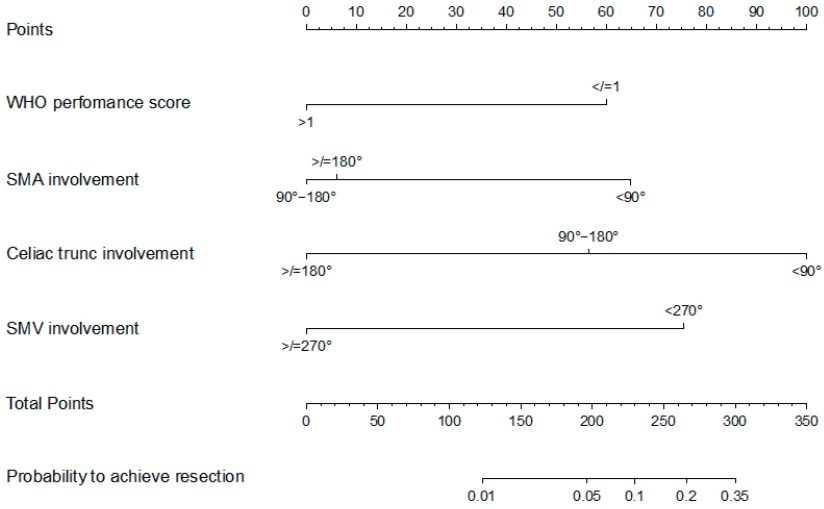


Figure 3b. Nomogram for the probability of resection in patients with locally advanced pancreatic cancer starting treatment with FOLFIRINOX
WHO performance score indicates World Health Organization performance score, SMA indicates superior mesenteric artery, and SMV indicates superior mesenteric vein.

DISCUSSION

This multicenter study developed and internally validated two nomograms to predict survival and tumor resection after first line treatment with FOLFIRINOX in a multicenter cohort of patients with LAPC. The model for 1-year and 2-year OS included older age, female sex, CCI score ≤1, and serum CA 19.9 ≤274 U/ml as positive prognostic factors with a good calibration and reasonable discrimination. The model to predict resection included WHO performance score ≤1, and vascular involvement of the SMA, celiac trunk and SMV, with a good calibration and good discrimination. Both nomograms include data that are readily available in daily practice and are easy to use.

Only two other studies have developed nomograms to predict outcomes in patients with LAPC. One presented a nomogram in patients with LAPC (combined with borderline resectable tumors) who were mostly treated with gemcitabine based chemoradiation. In this model, a radiotherapeutic dose ≥61Gy, surgical resection, pre-treatment maximum standardized uptake value (SUV_{max}) <3.5 (on PET-CT), and pre-treatment serum CA 19.9 ≤400 U/mL predicted an improved overall survival.[21] Another nomogram, based on baseline variables, in patients treated with gemcitabine based chemotherapy or chemoradiation suggested age, tumor size, albumin, pain, and elevated serum CA 19.9 as predictors for overall survival.[22] None of these nomograms, however, were developed for treatment with FOLFIRINOX, whereas this is nowadays the preferred chemotherapy in patients with LAPC.

Surprisingly, higher age was associated with better survival in our model. Most other studies have suggested that age has no influence on overall survival, or that a younger age predicts better outcomes.[22-24] An explanation for this unexpected finding is the inclusion of only very fit elderly patients with a favorable prognosis who are deemed eligible for treatment with FOLFIRINOX. Some studies regarding other types of cancer suggest younger patients to have a worse prognosis, due to more aggressive subtypes.[25,26] Our finding that female sex was associated with improved survival has been previously suggested by others, especially in patients treated with FOLFIRINOX.[27-29] The other factors that were found to be associated with longer survival, the CCI and serum CA 19.9 are known prognostic factors in pancreatic cancer.[30-33] High serum CA 19.9 levels might suggest micro-metastatic disease or a high disease load.[34] It has been shown that a decrease in serum CA 19.9 following induction therapy might be a predictor for prolonged survival.[35,36] Since the intention of this study was to develop nomograms that can be used before start of first line treatment with FOLFIRINOX, we only included baseline CA 19.9 levels.

The probability of undergoing tumor resection is predicted by a patients WHO performance score and vascular involvement of the tumor. In line with our findings, the influence of the performance status on probability of a resection has been previously reported, with a lower performance score leading to an increased possibility of resection.[12,37] Currently, the decision to perform a resection in patients with LAPC is mostly based on anatomic criteria, such as vascular involvement according to the NCCN criteria determined on radiographic imaging.[3,12] This factor was therefore not surprisingly associated with resection in our model. The model shows that arterial involvement >90° already substantially decreases the probability of a resection, as compared to <90° contact, which can be relevant information when consulting a patient at diagnosis. After induction chemotherapy with FOLFIRINOX, it may be difficult to evaluate vascular involvement on imaging, since fibrosis can be confused with residual tumor.[38,39] In line with our findings, previous studies described tumor involvement of the SMA as a worse predictor for the probability of resection.[7,40] The unexpected finding that 90°-180° involvement of the SMA is a slightly worse predictor than >180° involvement might be explained by the relative small patient group who underwent tumor resection with SMA involvement. Involvement of the celiac trunk is not always a contra-indication for resection. Pancreatic neck or body tumors can be resected by performing an Appleby procedure (i.e. distal pancreatectomy with celiac artery resection (DP-CAR)).[41] This, however, is not possible for pancreatic head tumors. Extensive and proximal involvement of the SMV might decrease the probability of a resection because of involvement of the proximal jejunal veins, hampering venous reconstruction.[3,42] The decision to proceed to surgery after induction chemotherapy is often a difficult decision in clinical practice.[1] The use of the baseline imaging in the developed nomogram might support the decision-making process after neoadjuvant therapy and manage patients' expectations regarding the probability of resection.

Nowadays, newer chemotherapeutic regimens, especially FOLFIRINOX, are recommended as first line treatment for patients with LAPC, with a promising increase in OS.[5,37,43] In our cohort, 13% of patients underwent resection after FOLFIRINOX treatment, with a median OS of 23 months. We included all consecutive patients diagnosed with LAPC and starting treatment with FOLFIRINOX, in a multicenter setting. This might explain the lower, but perhaps more realistic outcome with respect to resection rate, similar to the 9% resection rate described in another unselected cohort of patients treated with four different chemotherapeutic regimens.[8] Even though these more realistic outcomes show improved survival in resected patients, it is important to take into consideration that patients with LAPC undergoing resection represent a highly selected population. The higher resection rates and improved survival in previous studies are mostly based on the patient population from single centers. Furthermore, it is not known if these patients would have

had the same survival benefit when treated with FOLFIRINOX only.[44] No randomized trial has been performed to investigate the benefit of a resection after FOLFIRINOX treatment in terms of survival. It should therefore be noted that the main goal of FOLFIRINOX treatment in patients with LAPC is to increase survival and quality of life, rather than achieving surgical resection.

Our study has several limitations. First, the number of patients undergoing resection was relatively small, which might have caused overfitting of the model. We still developed the nomogram for resection because our cohort is one of the largest cohorts including consecutive patients diagnosed with LAPC who started first line treatment with FOLFIRINOX. Thereby, this study reflects the current clinical practice as much as possible and minimizes the possibility of bias. Although the number of events was small, the model demonstrated a good predictive accuracy after internal validation. Subsequent external validation of the model is, however, needed. A second limitation of our study refers to the performance of the nomogram predicting OS. Patients with LAPC demonstrate a small survival distribution, since the majority of these patients have a poor prognosis. This might explain the relatively low c-index and reasonable discrimination for 2-year survival. This is, however, the first nomogram reported to predict OS in patients with LAPC, who are eligible and willing to start treatment with FOLFIRINOX. Since nomograms are increasingly used in daily clinical practice, especially in the treatment of oncologic patients[14], we believe this information can be useful in the discussion between the patient and their physician whether to start treatment with FOLFIRINOX or not. And third, in the Netherlands the DPCG criteria[1,6] are used to diagnose patients with LAPC. All patients, however, are evaluated according to the NCCN criteria[3] after induction chemotherapy. This will lead to more patients receiving induction chemotherapy, but will not deprive patients from their possibility for a resection.

CONCLUSIONS

In conclusion, the proposed nomograms for the prediction of OS and tumor resection may support the shared decision-making process and manage expectations in patients with LAPC undergoing treatment with FOLFIRINOX. Both nomograms will be freely available on www.pancreascalculator.nl after publication.

AUTHOR CONTRIBUTION

LJHB, MSW, IQM and HCvS contributed to the conception and design of the work. All authors contributed to patient recruitment and data acquisition. LJHB, MSW, LAD, SvR and HCvS performed statistical analysis and data analysis. LJHB drafted the manuscript. All authors had substantial contribution to interpretation of the data, added important intellectual content to the work and approved the final version of the manuscript. All authors agree to be accountable for all aspects of the work and agree that no questions remain related to the accuracy or integrity of any part of the work.

DISCLOSURE OF CONFLICTS

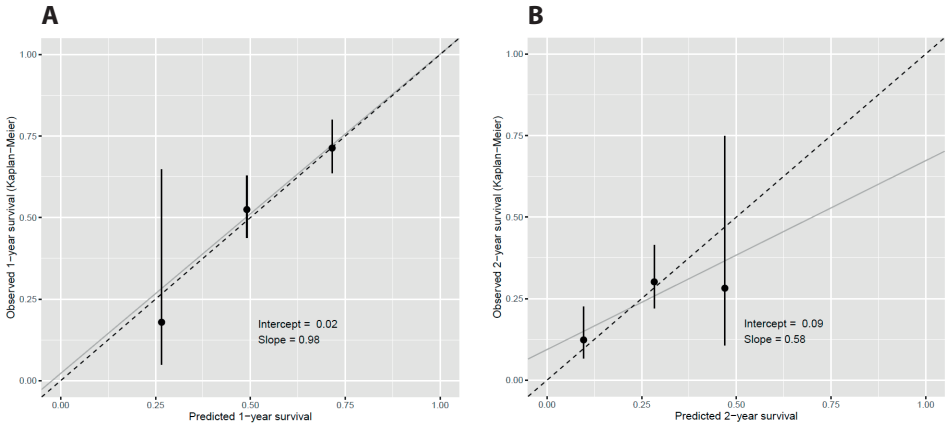
The authors have no financial interest in relation to this work.

REFERENCES

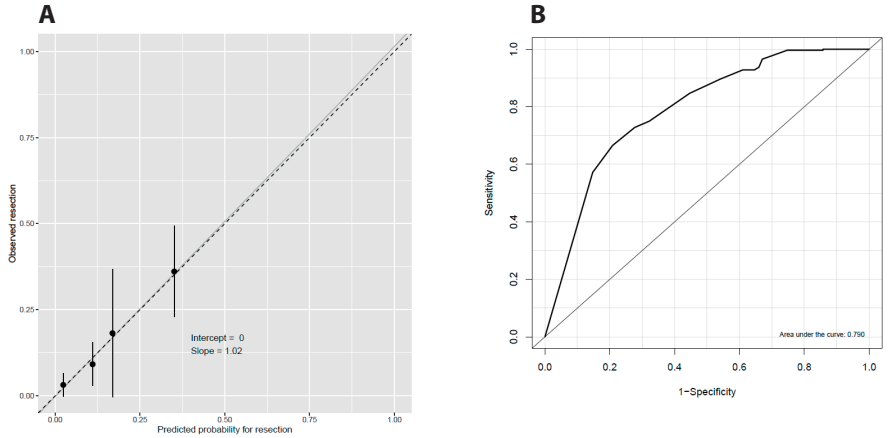
1. Reames BN, Blair AB, Krell RW, et al. Management of Locally Advanced Pancreatic Cancer: Results of an International Survey of Current Practice. Ann Surg. Published online August 2019.
2. Philip PA. Locally advanced pancreatic cancer: where should we go from here? J Clin Oncol. 2011;29(31):4066-4068.
3. Tempero MA, Malafa MP, Al-Hawary M, et al. Pancreatic Adenocarcinoma, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2017;15(8):1028-1061.
4. Abendroth A, Noureddine R, Abramczyk M, et al. Long-term outcome of patients with advanced pancreatic cancer treated with sequential chemotherapies before the era of modern combination therapy protocols. J Cancer Res Clin Oncol. 2019;145(2):445-455.
5. Suker M, Beumer BR, Sadot E, et al. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. Lancet Oncol. 2016;17(6):801-810.
6. Rombouts SJ, Walma MS, Vogel JA, et al. Systematic Review of Resection Rates and Clinical Outcomes After FOLFIRINOX-Based Treatment in Patients with Locally Advanced Pancreatic Cancer. Ann Surg Oncol. 2016;23(13):4352-4360.
7. Sadot E, Doussot A, O'Reilly EM, et al. FOLFIRINOX Induction Therapy for Stage 3 Pancreatic Adenocarcinoma. Ann Surg Oncol. 2015;22(11):3512-3521.
8. Maggino L, Malleo G, Marchegiani G, et al. Outcomes of Primary Chemotherapy for Borderline Resectable and Locally Advanced Pancreatic Ductal Adenocarcinoma. JAMA Surg. Published online July 2019.
9. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817-1825.
10. Rombouts SJ, Mungroop TH, Heilmann MN, et al. FOLFIRINOX in Locally Advanced and Metastatic Pancreatic Cancer: A Single Centre Cohort Study. J Cancer. 2016;7(13):1861-1866.
11. Hackert T, Sachsenmaier M, Hinz U, et al. Locally Advanced Pancreatic Cancer: Neoadjuvant Therapy With Folfirinox Results in Resectability in 60% of the Patients. Ann Surg. 2016;264(3):457-463.
12. Gemenetzis G, Groot VP, Blair AB, et al. Survival in Locally Advanced Pancreatic Cancer After Neoadjuvant Therapy and Surgical Resection. Ann Surg. 2019;270(2):340-347.
13. Marthey L, Sa-Cunha A, Blanc JF, et al. FOLFIRINOX for locally advanced pancreatic adenocarcinoma: results of an AGEO multicenter prospective observational cohort. Ann Surg Oncol. 2015;22(1):295-301.
14. Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than meets the eye. Lancet Oncol. 2015;16(4):e173-80.
15. Strijker M, Mackay TM, Bonsing BA, et al. Establishing and Coordinating a Nationwide Multidisciplinary Study Group: Lessons Learned by the Dutch Pancreatic Cancer Group. Ann Surg. 2020;271(4):e102-e104.
16. Versteijne E, van Eijck CHJ, Punt CJA, et al. Preoperative radiochemotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC trial): study protocol for a multicentre randomized controlled trial. Trials. 2016;17(1):127.
17. Amin M, Edge S, Greene F, Byrd D, Brookland R, Washington M. AJCC Cancer Staging Manual. 8th ed. Springer; 2017.
18. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-247.
19. Moons KGM, Wolff RF, Riley RD, et al. PROBAST: A Tool to Assess Risk of Bias and Applicability of Prediction Model Studies: Explanation and Elaboration. Ann Intern Med. 2019;170(1):W1-W33.
20. Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. BMJ. 2015;350:g7594.
21. Choi SH, Park SW, Seong J. A nomogram for predicting survival of patients with locally advanced pancreatic cancer treated with chemoradiotherapy. Radiother Oncol. 2018;129(2):340-346.
22. Vernerey D, Huguet F, Vienot A, et al. Prognostic nomogram and score to predict overall survival in locally advanced untreated pancreatic cancer (PROLAP). Br J Cancer. 2016;115(3):281-289.
23. Higuera O, Ghanem I, Nasimi R, Prieto I, Koren L, Feliu J. Management of pancreatic cancer in the elderly. World J Gastroenterol. 2016;22(2):764-775.
24. Castel-Kremer E, De Talhouet S, Charlois A-L, et al. An onco-geriatric approach to select older patients for optimal treatments of pancreatic adenocarcinoma. J Geriatr Oncol. 2018;9(4):373-381.

25. Chen H-L, Zhou M-Q, Tian W, Meng K-X, He H-F. Effect of Age on Breast Cancer Patient Prognoses: A Population-Based Study Using the SEER 18 Database. PLoS One. 2016;11(10):e0165409.
26. van Eeghen EE, Bakker SD, van Bochove A, Loffeld RJLF. Impact of age and comorbidity on survival in colorectal cancer. J Gastrointest Oncol. 2015;6(6):605-612. doi:10.3978/j.issn.2078-6891.2015.070
27. Vainshtein JM, Schipper M, Zalupski MM, et al. Prognostic significance of carbohydrate antigen 19-9 in unresectable locally advanced pancreatic cancer treated with dose-escalated intensity modulated radiation therapy and concurrent full-dose gemcitabine: analysis of a prospective phase 1/2 dose escala. Int J Radiat Oncol Biol Phys. 2013;86(1):96-101.
28. Peixoto RD, Speers C, McGahan CE, Renouf DJ, Schaeffer DF, Kennecke HF. Prognostic factors and sites of metastasis in unresectable locally advanced pancreatic cancer. Cancer Med. 2015;4(8):1171-1177.
29. Hohla F, Hopfinger G, Romeder F, et al. Female gender may predict response to FOLFIRINOX in patients with unresectable pancreatic cancer: a single institution retrospective review. Int J Oncol. 2014;44(1):319-326.
30. Cai S, Hong TS, Goldberg SI, et al. Updated long-term outcomes and prognostic factors for patients with unresectable locally advanced pancreatic cancer treated with intraoperative radiotherapy at the Massachusetts General Hospital, 1978 to 2010. Cancer. 2013;119(23):4196-4204.
31. Dohopolski MJ, Glaser SM, Vargo JA, Balasubramani GK, Beriwal S. Stereotactic body radiotherapy for locally-advanced unresectable pancreatic cancer-patterns of care and overall survival. J Gastrointest Oncol. 2017;8(5):766-777.
32. Park HM, Park S-J, Han S-S, Kim SH. Surgery for elderly patients with resectable pancreatic cancer, a comparison with non-surgical treatments: a retrospective study outcomes of resectable pancreatic cancer. BMC Cancer. 2019;19(1):1090.
33. Nakai Y, Isayama H, Sasaki T, et al. Comorbidity, not age, is prognostic in patients with advanced pancreatic cancer receiving gemcitabine-based chemotherapy. Crit Rev Oncol Hematol. 2011;78(3):252-259.
34. Isaji S, Mizuno S, Windsor JA, et al. International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. Pancreatology. 2018;18(1):2-11.
35. van Veldhuisen E, Vogel JA, Klompmaker S, et al. Added value of CA19-9 response in predicting resectability of locally advanced pancreatic cancer following induction chemotherapy. HPB (Oxford). 2018;20(7):605-611.
36. Aoki S, Motoi F, Murakami Y, et al. Decreased serum carbohydrate antigen 19-9 levels after neoadjuvant therapy predict a better prognosis for patients with pancreatic adenocarcinoma: a multicenter case-control study of 240 patients. BMC Cancer. 2019;19(1):252.
37. Seufferlein T, Hammel P, Delpero JR, et al. Optimizing the management of locally advanced pancreatic cancer with a focus on induction chemotherapy: Expert opinion based on a review of current evidence. Cancer Treat Rev. 2019;77:1-10.
38. Katz MHG, Fleming JB, Bhosale P, et al. Response of borderline resectable pancreatic cancer to neoadjuvant therapy is not reflected by radiographic indicators. Cancer. 2012;118(23):5749-5756.
39. Verbeke C, Lohr M, Karlsson JS, Del Chiaro M. Pathology reporting of pancreatic cancer following neoadjuvant therapy: challenges and uncertainties. Cancer Treat Rev. 2015;41(1):17-26.
40. Bednar F, Zenati MS, Steve J, et al. Analysis of Predictors of Resection and Survival in Locally Advanced Stage III Pancreatic Cancer: Does the Nature of Chemotherapy Regimen Influence Outcomes? Ann Surg Oncol. 2017;24(5):1406-1413.
41. Klompmaker S, Peters NA, van Hilst J, et al. Outcomes and Risk Score for Distal Pancreatectomy with Celiac Axis Resection (DP-CAR): An International Multicenter Analysis. Ann Surg Oncol. 2019;26(3):772-781.
42. Hosokawa Y, Nagakawa Y, Sahara Y, et al. Surgical Outcomes of Pancreaticoduodenectomy for Pancreatic Cancer with Proximal Dorsal Jejunal Vein Involvement. J Gastrointest Surg. 2018;22(7):1179-1185.
43. Springfeld C, Jager D, Buchler MW, et al. Chemotherapy for pancreatic cancer. Presse Med. 2019;48(3 Pt 2):e159-e174.
44. Reni M, Zanon S, Balzano G, et al. Selecting patients for resection after primary chemotherapy for non-metastatic pancreatic adenocarcinoma. Ann Oncol Off J Eur Soc Med Oncol. 2017;28(11):2786-2792.

SUPPLEMENTARY MATERIAL



Supplemental Figure 1. Calibration slopes of the model for (a) 1-year overall survival, and (b) 2-year overall survival Perfect prediction corresponds to the 45° line. The grey line corresponds to the observed prediction.

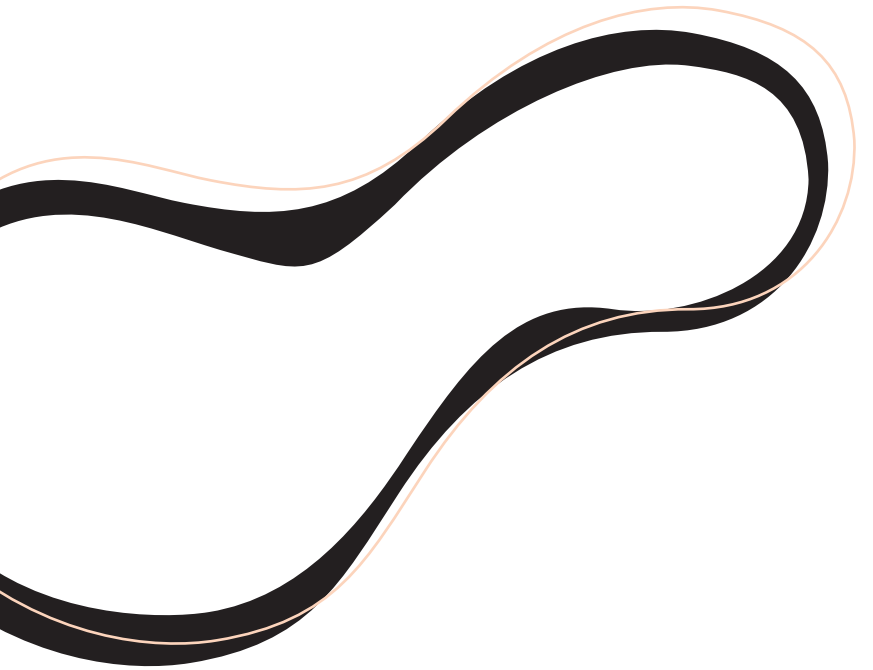


Supplemental Figure 2. (a) Calibration slope and (b) ROC-curve of the model for resection
(a) Perfect prediction corresponds to the 45° line. The grey line corresponds to the observed prediction.

Supplemental table 1. Postoperative outcomes of patients with locally advanced pancreatic cancer following tumor resection after FOLFIRINOX

	All n= 32	**(%)**
Type of resection		
Whipple	25	(78)
Distal pancreatectomy	1	(3)
DP-CAR	4	(13)
Total pancreatectomy	2	(6)
Postoperative complications		
≤Clavien-Dindo grade 2	9	(28)
≥Clavien-Dindo grade 3	17	(53)
Ninety-day mortality	1	(3)
Tumor size (in pathology report), mm, median [IQR][a]	29 [25-39]	
Resection margin		
R0	17	(53)
R1	15	(47)
Amount of lymph nodes harvested, median [IQR]	18 [13-27]	
Positive lymph nodes, median [IQR]	1 [0-2]	

[a]2 missing; IQR, interquartile range; DP-CAR, distal pancreatectomy with celiac artery resection.



Chapter 6

Added value of intra-operative ultrasound to determine the resectability of locally advanced pancreatic cancer following FOLFIRINOX chemotherapy (IMAGE): a prospective multicenter study

HPB (Oxford), October 2019; 21(10):1385-1392

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ABSTRACT

Background

Determining the resectability of locally advanced pancreatic cancer (LAPC) after FOLFIRINOX chemotherapy is challenging because CT-scans cannot reliably assess vascular involvement. This study evaluates the added value of intra-operative ultrasound (IOUS) in LAPC following FOLFIRINOX induction chemotherapy.

Methods

Prospective multicenter study in patients with LAPC who underwent explorative laparotomy with IOUS after FOLFIRINOX chemotherapy. Resectability was defined according to the National Comprehensive Cancer Network guidelines. IOUS findings were compared with preoperative CT-scans and pathology results.

Results

CT-staging in 38 patients with LAPC after FOLFIRINOX chemotherapy defined 22 patients LAPC, 15 borderline resectable and one resectable. IOUS defined 19 patients LAPC, 13 borderline resectable and six resectable. In 12/38 patients, IOUS changed the resectability status including five patients from borderline resectable to resectable and five patients from LAPC to borderline resectable. Two patients were upstaged from borderline resectable to LAPC. Tumor diameters were significantly smaller upon IOUS (31.7 ± 9.5 mm versus 37.1 ± 10.0 mm, p=0.001) and resectability varied significantly (p=0.043). Ultimately, 20 patients underwent resection of whom 14 were evaluated as (borderline) resectable on CT-scan, and 17 on IOUS.

Conclusion

This prospective study demonstrates that IOUS may change the resectability status up to a third of patients with LAPC following FOLFIRINOX chemotherapy.

INTRODUCTION

Pancreatic cancer is notorious for its limited treatment options and poor survival.[1] Surgical resection combined with (neo-)adjuvant chemotherapy offers the best chance of long-term survival.[2] This combination is, however, only feasible in approximately 10% of patients, as 60% of patients present with metastatic disease, 30% with locally advanced, unresectable pancreatic cancer (LAPC) and half of patients do not receive adjuvant chemotherapy after resection.[3,4]

In LAPC, an upfront radical (R0) resection is not possible due to extensive perivascular tumor infiltration.[2] Recent studies demonstrate that in 25–30% of patients with LAPC treated with FOLFIRINOX chemotherapy (a combination of 5-fluorouracil, oxaliplatin, leucovorin and irinotecan), the tumor can be downstaged to (borderline) resectable disease.[5] Response evaluation following FOLFIRINOX is, however, difficult as computed tomography (CT) imaging cannot reliably differentiate viable tumor infiltration from post-chemotherapeutic desmoplastic reaction.[6,7] This is currently one of the major challenges in the treatment of LAPC. As a result of this low diagnostic accuracy, some experts now advocate routine surgical exploration in all patients with LAPC with radiological non-progressive disease following FOLFIRINOX.[7,8]

During surgical exploration, however, it is often still difficult to determine resectability. Multiple biopsies are typically sent for frozen section to support this process, but this is very time consuming as it requires extensive dissection and may increase morbidity. Therefore there is a need for diagnostic tools that can accurately determine the extent of vascular tumor infiltration during explorative surgery.

Due to its high spatial resolution, intra-operative ultrasound (IOUS) might be of additional value when defining vascular involvement and has previously been used for other tumors to determine resectability during surgical exploration with promising results.[9] The aim of this study was to compare the outcomes of IOUS, with preoperative CT-scan and surgical exploration in patients with LAPC who were treated with induction FOLFIRINOX chemotherapy.

METHODS

This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[10] The IMAGE study included patients in whom upfront radical resection was considered not feasible and who had received FOLFIRINOX induction chemotherapy, followed by exploratory laparotomy in five centers of the

Dutch Pancreatic Cancer Group (DPCG) between April 2016 and January 2018. At the start of surgical exploration, prior to any dissection, IOUS was performed by an experienced interventional radiologist.

Post-FOLFIRINOX resectability was defined according to the National Comprehensive Cancer Network (NCCN) guidelines.[11] Resectable disease was defined as the absence of arterial tumor contact (of the celiac trunk, superior mesenteric artery or hepatic artery) and tumor contact with the superior mesenteric vein or portal vein ≤180° without contour irregularity. Borderline resectable disease was defined as a maximum of 180° of arterial contact and/or reconstructable venous involvement (of the porto-mesenteric vein).[11] LAPC was defined as >180° arterial contact and/or unreconstructable venous involvement. Patients with (borderline) resectable disease after chemotherapy or with LAPC undergoing local ablative treatment requiring laparotomy were considered eligible for surgical exploration with IOUS. Metal stents were not considered a contra-indication for IOUS. Patients with progressive disease after induction chemotherapy, according to the Response Evaluation Criteria In Solid Tumors (RECIST),[12] were excluded from surgical exploration, independently of their resectability status on CT-scan. In case of metastases during surgical exploration, patients were excluded from this study and no further exploration was performed.

All post-FOLFIRINOX CT-scans consisted of a chest and abdominal CT-scan according to a biphasic protocol with a late arterial phase (35–40 s after intravenous contrast injection) and a late portal phase (60–70 s after intravenous contrast injection). CT-scans are performed on a Siemens Sensation 64-slice CT-scanner after injection of 1.5–2.0 ml/kg (with a maximum of 120 ml) Ultravist (Bayer) contrast medium with an injection rate of 3.5 ml/s. Only axial images and coronal and sagittal reconstructions were used for the evaluation of the CT-scans. Tumor characteristics including diameters in three directions, visceral extent, vascular tumor involvement and consequently resectability were scored with predefined scoring forms (Appendix 1), by a centralized expert panel consisting of three experienced abdominal radiologists (with at least 4 years of experience) and an experienced pancreatic surgeon. The radiologists who scored the restaging CT-scans did not perform IOUS in the present study.

In all cases, IOUS was performed with a high frequency 12 mHz linear probe (Esaote, Genua, Italy or Philips Epiq 5, Eindhoven, the Netherlands), directly placed on the surface of the pancreas after laparotomy, or on the stomach if a transgastric approach was preferred by the radiologist. The IOUS procedures of the pancreas were performed by dedicated abdominal radiologists trained for IOUS by a proctor or by the proctor himself. Prior to the present study, the proctor had already performed >40 IOUS procedures of patients with

LAPC following induction chemotherapy. Tumor characteristics were assessed using a standardized IOUS protocol with the same scoring form as was used for CT-evaluation to reduce the chance of interpretation bias by the radiologists (Appendix 1).
Typically, tissue with a hypoechoic aspect on IOUS was scored as tumor tissue, whereas vessel walls and surrounding fat tissue are often hyperechoic due to the reflection of ultrasound waves (Figure 1). Vascular structures were scored not involved with viable tumor if no interruption of the hyper-echoic vascular wall was observed upon IOUS. All surgical procedures were performed in high-volume centers (i.e. performing >20 pancreatoduodenectomies annually). Both CT, IOUS and surgical exploration findings were taken into consideration before deciding to perform a resection. Resected specimens were pathologically assessed for radicality including vascular resection margins. A radical resection margin (R0) was defined as a tumor-free resection margin of at least 1 mm in all directions, according to the Royal College of Pathologists definition.[13]

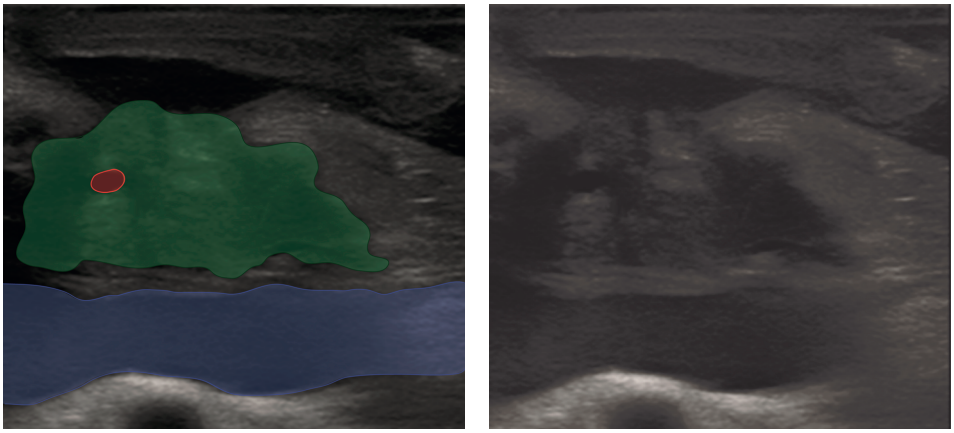

Figure 1. Intra-operative ultrasound in a patient with pancreatic cancer and >270° portal vein involvement on CT-scan. IOUS images to illustrate differentiation between hypo-echoic tumor tissue (green) and hyper-echoic tissue between the portal vein (blue) and tumor (green). Hepatic artery is shown in red. The IOUS demonstrates that the portal vein has no tumor infiltration.

Statistical analysis

Continuous data are presented as means and standard deviations (SD) in case of a normal distribution, or as medians and interquartile ranges (IQR) in case of a non-normal distribution. Categorical data (binary, ordinal and nominal) are presented as frequencies and percentages. Paired samples T-test was used to compare means. Resectability status was compared between the two modalities using a two-sided McNemar–Bowker test

of symmetry. Diagnostic accuracy for resectability could not accurately be determined as the IOUS findings were used in the decision making process to proceed with a resection. Moreover, a golden reference standard (i.e. pathological proof) was not always available for patients who did not undergo resection. A p-value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows version 24.0 (IBM Corp., Orchard Road Armonk, New York, US).

RESULTS

A total of 38 patients with LAPC were included with a mean age of 63 ± 8 years. This included 27 tumors of the pancreatic head/uncinate process, nine of the pancreatic body and two of the pancreatic tail. Twenty-three patients were female. Median CA19-9 at diagnosis was 140 U/mL (IQR 40–396). Patients received a median of four cycles (IQR 4-4) of FOLFIRINOX prior to surgical exploration. Because of toxicity, one patient switched to a combination of gemcitabine with nab-paclitaxel after two courses of FOLFIRINOX prior to restaging.

At restaging, 6/38 patients were classified as having a RECIST partial response and 32/38 as having RECIST stable disease. Median CA19-9 decreased to 78 U/mL (IQR 17–135) in 28 patients of whom CA19-9 levels were available pre-and post-chemotherapy. Of these, 18/28 had a decrease in CA19-9 of at least 30%.[14] Based on the preoperative CT-scan, 22 patients were defined as LAPC, 15 as borderline resectable and one patient as resectable. Median time between CT-restaging (i.e. within 1–2 weeks after the last cycle of chemotherapy) and surgery was four weeks (IQR 3–5).

During explorative laparotomy, IOUS typically demonstrated smaller tumor diameters (31.7 ± 9.5 mm versus 37.1 ± 10.0 mm, p=0.001) and in most cases also less extensive vascular infiltration compared with the last preoperative CT-scan (Table 1). Upon IOUS, 19 patients were defined as LAPC, 13 as borderline resectable and six patients as resectable. Consequently, IOUS changed the resectability status in 12/38 patients. Five patients with borderline resectable disease on CT-scan were deemed primary resectable on IOUS. Of these patients, two showed less involvement of the superior mesenteric artery (SMA) as well as the porto-mesenteric vein (PMV) when using IOUS. Two patients demonstrated less involvement of the common hepatic artery (CHA) and the PMV compared to CT-scan and one patient showed limited involvement of the SMA and CHA. Five patients with LAPC on CT-scan were deemed borderline resectable on IOUS due to less involvement of the CHA and PMV in two cases, the SMA and CHA in one case, less involvement of the PMV in one case and less extensive involvement of arterial

Table 1. Tumor characteristics upon preoperative CT and intra-operative ultrasound imaging in 38 patients with locally advanced pancreatic cancer

Imaging modality	CT (n=38)	IOUS (n=38)
Size in mm, mean (sd)	37 (10)	32 (9)
Arterial involvement, no.		
Celiac Trunk		
No contact	32	32
1-180°	1	2
>180°	5	4
Hepatic Artery		
No contact	21	29
1-180°	11	4
>180°	6	5
Superior Mesenteric Artery*		
No contact	11	21
1-180°	15	8
>180°	11	8
Venous involvement, no.		
Porto-Mesenteric Vein		
No contact	2	8
1-180°	26	20
>180°	10	10

***** From one patient the degrees of SMA contact could not be evaluated ; sd: standard deviation; mm: millimetre; IOUS: intra-operative ultrasound; CT: computed-tomography imaging.

jejunal branches of the SMA in the last case. Two patients with borderline resectable disease on CT-scan had LAPC according to IOUS (Table 2). The patients who were evaluated as LAPC upon IOUS (and borderline resectable on CT-scan) demonstrated more extensive involvement of a collateral connecting the superior mesenteric artery with the hepatic artery in one case and more extensive involvement of the common hepatic artery in the second case. The first patient did not undergo resection after frozen sections demonstrated vital tumor tissue surrounding the collateral feeding the hepatic artery. The second patient did undergo resection (total pancreatectomy), after frozen sections demonstrated no vital tumor tissue surrounding the common hepatic artery. Upon statistical analysis, resectability status was scored significantly different between the two modalities (p=0.043). An example of the discrepancy between CT-scan and IOUS is shown in Figure 2.

Table 2. NCCN resectability status according to the preoperative CT-scan and intra-operative ultrasound

		IOUS-staging			
		Resectable	**Borderline**	**LAPC**	**Total**
CT-staging	Resectable	1	0	0	1
	Borderline	5	8	2	15
	LAPC	0	5	17	22
	Total	6	13	19	38

IOUS: intra-operative ultrasound; CT: computed-tomography imaging; LAPC: locally advanced pancreatic cancer. Gray demarcation indicates a difference in resectability status between IOUS and CT-scan. Resectability status varied significantly between the two modalities (p=0.043).

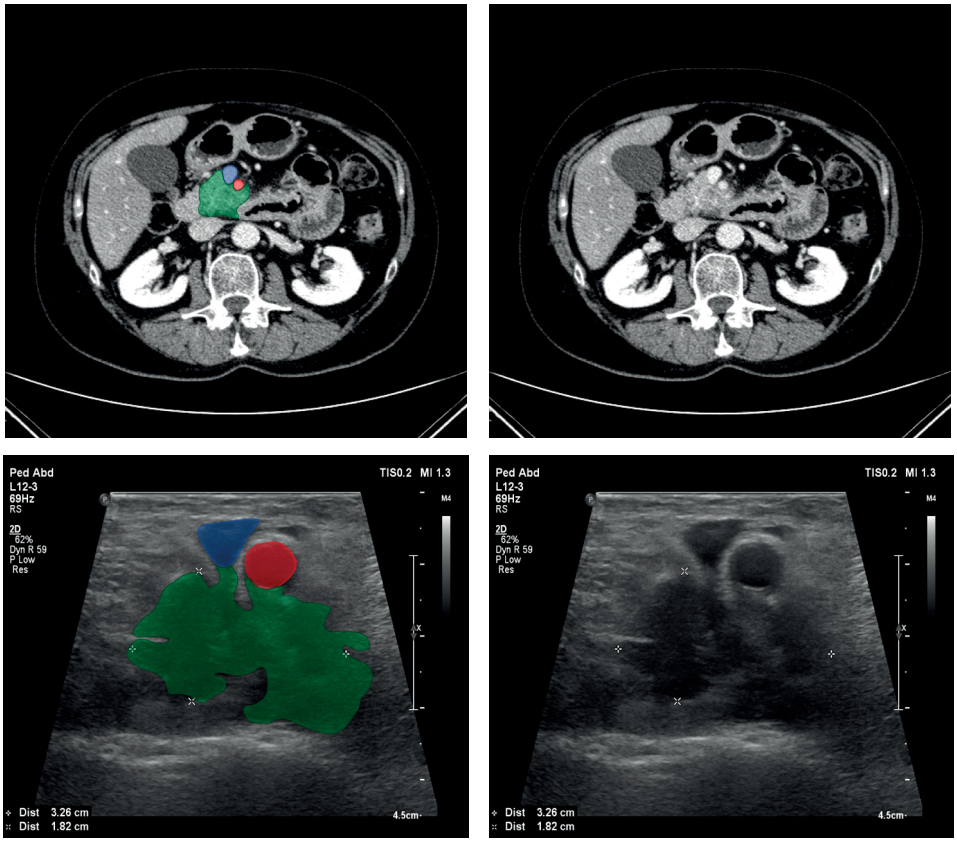

Figure 2. Preoperative CT-scan and IOUS in a patient with pancreatic cancer after 4 cycles of FOLFIRINOX. Upper images: Upon CT-scan, 90–180° tumor infiltration (green) was seen around the superior mesenteric vein (blue) and 180–270° contact with the superior mesenteric artery (red), rendering this patient unresectable.
Lower images: Upon IOUS less tumor infiltration was seen: <90° (green) around the superior mesenteric vein (blue) and 90–180° with the superior mesenteric artery (red), rendering this patient borderline resectable.

Twenty patients finally underwent resection and 18 patients had unresectable disease during exploration. An R0-resection was achieved in 8/20 patients. Of the 20 resections, 14 were judged as (borderline) resectable on CT-scan, and 17 as (borderline) resectable on IOUS. Two patients underwent resection despite being diagnosed as NCCN LAPC upon CT-scan and IOUS. Both patients had tumor infiltration of the first jejunal branches of the superior mesenteric vein. However, it was considered borderline resectable by the surgeon, and a resection was performed. For the remaining patient that was upstaged from borderline resectable on CT-scan to unresectable on IOUS, a resection was proceeded after frozen section investigation showed no evidence for vital adenocarcinoma around the hepatic artery (i.e. desmoplastic reaction). Of the eight patients with an R0 resection, five were evaluated as (borderline) resectable on CT-scan and seven as (borderline) resectable on IOUS (Table 3).

Table 3. Resectability on IOUS and CT-scan versus surgical radicality

		Resectability on CT-scan		**Total**
		Unresectable	**(borderline) Resectable**	
	No	16	2	18
Underwent resection?	Yes, R0	3	5	8
	Yes, R1	3	9	12
Total		22	16	38
		Resectability on IOUS		**Total**
		Unresectable	**(borderline) Resectable**	
	No	16	2	18
Underwent resection?	Yes, R0	1	7	8
	Yes, R1	2	10	12
Total		19	19	38

IOUS: intra-operative ultrasound; CT: computed-tomography imaging; R0: radical resection; R1: irradical resection.

DISCUSSION

It is well known that CT-scans cannot accurately determine the extent of vascular involvement of pancreatic cancer after FOLFRINOX treatment. This first prospective multicenter study shows that IOUS may be helpful during surgical exploration of LAPC after FOLFIRINOX chemotherapy as it changed the resectability status based on CT-scan in approximately one-third of the patients.

Previous studies have suggested that IOUS can accurately determine the vascular involvement in chemo-naïve patients with pancreatic cancer, with a sensitivity and specificity of 92% and 93% respectively.[15] Until now, no studies investigated the diagnostic accuracy of IOUS in patients after neoadjuvant chemotherapy. This may especially be relevant in patients treated with FOLFIRINOX, since previous studies have shown that CT-scan is not accurate enough in this setting.[7,16] A major downside of IOUS is that it requires exploratory laparotomy and hence does not contribute to the selection procedure in advance of the surgical exploration, it may provide valuable information to facilitate the decision to proceed with a resection intra-operatively. During surgical exploration, surgeons highly valued the additional real-time information on vascular tumor involvement as more focus could be applied to the most endangered resection margins. This facilitates both the targeted sampling of tissue for frozen section, and the decision to proceed with exploration and can therefore avoid unnecessary dissection and associated morbidity.

The RECIST-criteria are often used to describe tumor response following induction chemotherapy and are used together with the vascular involvement to select patients for surgical exploration.[12] However, a partial response according to RECIST in pancreatic cancer after FOLFIRINOX is difficult to objectify with CT. This may lead to missed opportunities to resect. Previous prospective series showed only a 40% sensitivity of a CT-based RECIST partial response for resectability in patients with LAPC following induction chemotherapy[14] and no correlation with tumor size decrease with R0 resection.[6] In addition, vascular involvement and thus resectability is not accurately measured by CT-scan after FOLFIRINOX therapy.[7] As was also demonstrated in the present study, only six patients showed a partial response on CT, with 1/6 patients being classified as resectable and 2/6 as borderline resectable. Nevertheless, 20 patients ultimately underwent a resection, demonstrating the low sensitivity of CT-scans for resectability of LAPC after FOLFIRINOX. As neoadjuvant treatment is increasingly administered to patients with LAPC, future studies should focus on improving the selection of patients with initial LAPC treated with FOLFIRINOX for surgical exploration. A factor that may be of added value in this setting is regression of tumor-vessel contact as described by Cassinotto *et al*.[6] This prospective study found a decrease in tumor-vessel contact to be a reliable predictor of resectability after chemo-radiotherapy in patients with LAPC irrespective of the tumor diameter or the degree of residual vascular involvement. These results seem promising and ought to be validated in a cohort of patients with LAPC treated with FOLFIRINOX chemotherapy.

Another procedure that may contribute to the more accurate selection of patients for surgical exploration is endoscopic ultrasound (EUS). Previous studies have suggested

that EUS can more accurately determine vascular involvement of pancreatic cancer than CT-imaging in chemo-naïve patients.[17,18] In addition, EUS may allow for targeted tissue sampling trough fine-needle aspiration to distinguish between vital tumor and fibrosis. Future studies should assess the diagnostic accuracy of EUS for resectability in patients with LAPC treated with (FOLFIRINOX) induction chemotherapy, in order to reduce the rate of futile surgical explorations in these patients. Besides anatomical factors (i.e. tumor response, vascular involvement), biological criteria may be of great importance in the selection of patients for surgery.[19] Biomarkers such as CA19-9 and plasma microRNAs have been previously described to be useful in selecting patients for surgery after induction chemotherapy and should be used in addition to current imaging modalities.[14,20,21]

The results of this study should be interpreted in light of several limitations. First, this was a non-blinded study, since the performing radiologist was aware of the outcomes of the restaging CT-scans. This is, however, similar to clinical practice and this study was therefore deliberately not designed as a head-to-head comparison of IOUS with CT. Second, although pathological results from resected patients were available, intra-operative pathological confirmation of the exact IOUS findings (i.e. the differences between IOUS and CT assessment) was not routinely performed when resection was not performed. Therefore diagnostic accuracy tests (e.g. sensitivity, specificity for resection) could not be performed.

Currently the prospective multicenter ULTRAPANC study is pending in the Netherlands, which will assess the diagnostic accuracy of IOUS using standardized scoring methods and pathology as reference standard in patients undergoing explorative laparotomy for pancreatic cancer. Third, five out of 11 patients with a different resectablility status after IOUS already had (borderline) resectable disease on CT-scan. The clinical relevance of IOUS in this category of patients can be discussed since these patients may also have undergone a resection without IOUS. Fourth, although IOUS predicted resectability more often than CT-scan, the actual R0 rate was only 40% in the present cohort, demonstrating that radical resections remain challenging in patients with LAPC. Compared with previously published series, this proportion may be low.[22] An explanation could be that the patients in the present study only received four cycles of FOLFIRINOX prior to surgery. Although the evidence to support this hypothesis is limited, it might be that eight cycles of FOLFIRINOX and/or adding radiotherapy to the induction scheme further improves the R0-rate in these patients.[23,24] However, patients undergoing resection after induction chemotherapy may still benefit from an R1 resection.[25] Although the R0 rate was only 57% in the cohort study by Vogel *et al*., median overall survival of the resected patients was still 34 months (versus 15 months for non-resected

patients).[25] Finally, the delay of several weeks between CT-restaging and exploration may have allowed for tumor progression. However, this bias cannot explain the fact that IOUS mainly down-staged patients to (borderline) resectable disease. Strengths of this study include the prospective study design, the multicenter approach in consecutive patients with initial unresectable disease and the standardized reporting of both CT and IOUS outcomes scored by dedicated abdominal radiologists.

Taking these considerations in account, the current results imply that IOUS is a promising tool to determine resectability and support the process of surgical exploration of LAPC following FOLFIRINOX chemotherapy. Although the exact diagnostic value of IOUS should be established in future, larger studies, the present study shows that IOUS is capable of providing valuable information to the surgeon, changing the resectability status in a third of patients.

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CONFLICTS OF INTEREST

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REFERENCES

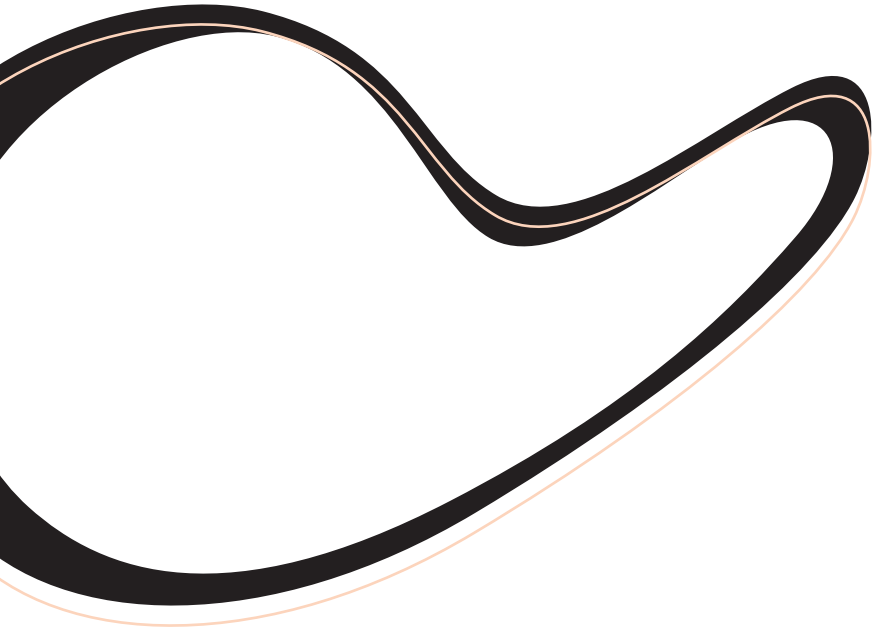
1. Hidalgo M. (2010) Pancreatic cancer. N Engl J Med 362:1605–1617.
2. Ducreux M, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goere D et al. (2015) Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 26:v56–v68.
3. Bakens MJ, van der Geest LG, van Putten M, van Laarhoven HW, Creemers GJ, Besselink MG et al. (2016) The use of adjuvant chemotherapy for pancreatic cancer varies widely between hospitals: a nationwide population-based analysis. Cancer Med 5:2825–2831.
4. Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. (2011) Pancreatic cancer. Lancet 378:607–620.
5. Rombouts SJ, Walma MS, Vogel JA, van Rijssen LB, Wilmink JW, Mohammad NH et al. (2016) Systematic review of resection rates and clinical outcomes after FOLFIRINOX-based treatment in patients with locally advanced pancreatic cancer. Ann Surg Oncol 23:4352–4360.
6. Cassinotto C, Mouries A, Lafourcade JP, Terrebonne E, Belleannee G, Blanc JF et al. (2014) Locally advanced pancreatic adenocarcinoma: reassessment of response with CT after neoadjuvant chemotherapy and radiation therapy. Radiology 273:108–116.
7. Ferrone CR, Marchegiani G, Hong TS, Ryan DP, Deshpande V, McDonnell EI et al. (2015) Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. Ann Surg 261:12–17.
8. Hackert T, Sachsenmaier M, Hinz U, Schneider L, Michalski CW, Springfeld C et al. (2016) Locally advanced pancreatic cancer: neoadjuvant therapy with folfirinox results in resectability in 60% of the patients. Ann Surg 264:457–463.
9. Marcal LP, Patnana M, Bhosale P, Bedi DG. (2013) Intraoperative abdominal ultrasound in oncologic imaging. World J Radiol 5:51–60.
10. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP et al. (2007) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 370:1453–1457.
11. Tempero MA, Arnoletti JP, Behrman SW, Ben-Josef E, Benson AB, 3rd, Casper ES et al. (2012) Pancreatic Adenocarcinoma, version 2.2012: featured updates to the NCCN Guidelines. J Natl Compr Cancer Netw 10:703–713.
12. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R et al. (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228–247.
13. The Royal College of Pathologists. (2017) Dataset for the histopathological reporting of pancreatic, ampulla of Vater and bile duct carcinoma. Available from: https://www.rcpath.org/resourceLibrary/g091-pancreasdataset-mar17.html.
14. van Veldhuisen E, Vogel JA, Klompmaker S, Busch OR, van Laarhoven HWM, van Lienden KP et al. (2018) Added value of CA19-9 response in predicting resectability of locally advanced pancreatic cancer following induction chemotherapy. HPB 20:605–611.
15. Shin LK, Brant-Zawadzki G, Kamaya A, Jeffrey RB. (2009) Intraoperative ultrasound of the pancreas. Ultrasound Q 25:39–48 [quiz].
16. Donahue TR, Isacoff WH, Hines OJ, Tomlinson JS, Farrell JJ, Bhat YM et al. (2011) Downstaging chemotherapy and alteration in the classic computed tomography/magnetic resonance imaging signs of vascular involvement in patients with pancreaticobiliary malignant tumors: influence on patient selection for surgery. Arch Surg 146:836–843.
17. Gress FG, Hawes RH, Savides TJ, Ikenberry SO, Cummings O, Kopecky K et al. (1999) Role of EUS in the preoperative staging of pancreatic cancer: a large single-center experience. Gastrointest Endosc 50:786–791.
18. Kala Z, Valek V, Hlavsa J, Hana K, Vanova A. (2007) The role of CT and endoscopic ultrasound in pre-operative staging of pancreatic cancer. Eur J Radiol 62:166–169.
19. Isaji S, Mizuno S, Windsor JA, Bassi C, Fernandez-Del Castillo C, Hackert T et al. (2018) International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. Pancreatology 18:2–11.
20. Meijer LL, Garajova I, Caparello C, Le Large TYS, Frampton AE, Vasile E et al. (2018 Nov 6) Plasma miR-181a-5p downregulation predicts response and improved survival after FOLFIRINOX in pancreatic ductal adenocarcinoma. Ann Surg. https://doi.org/10.1097/SLA.0000000000003084 [cited 2019 Mar 14]. [Epub ahead of print].

21. Tsai S, George B, Wittmann D, Ritch PS, Krepline AN, Aldakkak M et al. (2018 Oct 13) Importance of normalization of CA19-9 levels following neoadjuvant therapy in patients with localized pancreatic cancer. Ann Surg. https://doi.org/10.1097/SLA.0000000000003049 [cited 2019 Mar 14]. [Epub ahead of print].
22. Suker M, Beumer BR, Sadot E, Marthey L, Faris JE, Mellon EA et al. (2016) FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. Lancet Oncol 17:801–810.
23. Gemenetzis G, Groot VP, Blair AB, Laheru DA, Zheng L, Narang AK et al. (2018 Mar 30) Survival in locally advanced pancreatic cancer after neoadjuvant therapy and surgical resection. Ann Surg. https://doi.org/10.1097/SLA.0000000000002753 [cited 2019 Mar 14]. [Epub ahead of print].
24. Murphy JE, Wo JY, Ryan DP, Jiang W. (2018) Yeap BY, Drapek LC, et al. Total Neoadjuvant Therapy With FOLFIRINOX Followed by Individualized Chemoradiotherapy for Borderline Resectable Pancreatic Adenocarcinoma: a Phase 2 Clinical Trial. JAMA Oncol 4:963–969.
25. Vogel JA, Rombouts SJ, de Rooij T, van Delden OM, Dijkgraaf MG, van Gulik TM et al. (2017) Induction chemotherapy followed by resection or irreversible electroporation in locally advanced pancreatic cancer (IMPALA): a prospective cohort study. Ann Surg Oncol 24:2734–2743.

SUPPLEMENTARY MATERIAL

Appendix 1. CT-imaging and intra-operative ultrasound evaluation form

Tumor visible	No Yes					
Tumor localization		1. Head of pancreas / uncinate process 2. Body of pancreas 3. Tail of pancreas				
Largest tumor diameter	… mm					
Peri-pancreatic ingrowth	No Yes, please answer 1-9	1. Peripancreatic fat: a. Towards superior mesenteric artery b. Transverse mesocolon c. Mesenteric root d. Towards caval vein/aorta e. Cranially towards celiac trunk f. Dorsally of pancreatic body/tail g. Other: 2. Duodenum 3. Stomach 4. Hepatoduodenal ligament (i.e. common hepatic duct, hepatic artery, portal vein) 5. Jejunum 6. Colon 7. Left adrenal gland 8. Spleen 9. Other:				
Contact with superior mesenteric artery	No Yes, please answer 1-5	1. ≤90° 90°- ≤180° 180°- ≤270° >270° 2. Deformation: Yes No 3. Lumen reduction: No ≤50% >50% Occlusion 4. Tumor thrombus: Yes No 5. Length contact: … mm				
Contact with celiac trunk	No Yes, please answer 1-5	1. ≤90° 90°- ≤180° 180°- ≤270° >270° 2. Deformation: Yes No 3. Lumen reduction: No ≤50% >50% Occlusion 4. Tumor thrombus: Yes No 5. Length contact: … mm				
Contact with hepatic artery	No Yes, please answer 1-5	1. ≤90° 90°- ≤180° 180°- ≤270° >270° 2. Deformation: Yes No 3. Lumen reduction: No ≤50% >50% Occlusion 4. Tumor thrombus: Yes No 5. Length contact: … mm				
Contact with portal / superior mesenteric vein	No Yes, please answer 1-5	1. ≤90° 90°- ≤180° 180°- ≤270° >270° 2. Deformation: Yes No 3. Lumen reduction: No ≤50% >50% Occlusion 4. Tumor thrombus: Yes No 5. Length contact: … mm				
R0/R1 resection possible	No Yes Doubtful	If no or doubtful, please explain:				
Other remarks	No Yes					



Chapter 7

Occult metastases found during surgery in patients with presumed (borderline) resectable pancreatic cancer: development and external validation of a preoperative prediction model

Submitted

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ABSTRACT

Background

Occult metastatic disease is detected in a subset of patients during surgical exploration for presumed resectable pancreatic cancer. These patients are unnecessarily exposed to the risks of surgical exploration and often experience a delayed start of systemic therapy. This study aimed to develop and externally validate a model to preoperatively predict occult metastases in patients with potentially resectable pancreatic cancer.

Methods

Model development was performed with data from the nationwide Dutch Pancreatic Cancer Audit database, including all patients operated for presumed resectable and borderline resectable pancreatic cancer (January 2013 - December 2017). Multivariable logistic regression analysis was performed with pathologically proven distant metastases during surgery as outcome variable using a stepwise backward selection-method. The model was externally validated with a pancreatic surgery cohort from the University Hospital of Verona (January 2013 – December 2017).

Results

For model development, 2262 patients were included of whom 235 (10%) had occult metastases, located in the liver (n=143, 61%), peritoneal (n=73, 31%) or both (n=19, 8%). The final model included: age (OR 1.02, 95%CI 1.00-1.03), BMI (OR 0.96, 95%CI 0.93-0.99), pre-operative nutritional support (OR 1.73 95%CI 1.010-2.74), tumor diameter (OR 1.60, 95%CI 1.04-2.45), tumor composition (solid vs. cystic)(OR 2.33, 95%CI 1.20-4.35), indeterminate lesions on pre-operative imaging(OR 4.01, 95%CI 2.16-7.43). The prediction model showed a C-statistic of 0.65. External validation showed a poor discrimination with a C-statistic of 0.56 and poor calibration.

Conclusion

Although some predictor variables were significantly associated with occult metastases, the discrimination ability of the prediction model was only moderate and could not be confirmed by external validation. A staging laparoscopy should be considered more often since in this study the majority of occult metastases was found during primary laparotomy. Future biological and clinical markers, together with improved pre-operative imaging are needed.

INTRODUCTION

In Western Europe, pancreatic cancer has an incidence of 8.4 per 100 000 inhabitants and is estimated to become the second leading cause of cancer related death in the near future.[1,2] The majority of patients with pancreatic cancer have an advanced stage of disease at diagnosis, with only 10-20% qualifying for resection.[3,4] Current routine investigation for pre-operative staging includes a multidetector computed tomography (MDCT) using a dual-phase pancreatic protocol.[5] The accuracy of MDCT in determining resectability is 85-95%[5] and the main reason for unresectability during exploratory laparotomy is the presence of distant metastases that were not detected on pre-operative MDCT.[6] The reported incidence of occult distant metastases from recent studies is approximately 10-15%, of which the majority is located in the liver.[6,7]

Given the dismal prognosis of patients with metastatic pancreatic cancer, together with the possible delay in start of systemic treatment, it is important to avoid a futile laparotomy whenever possible. A potential valuable diagnostic tool to avoid unnecessary laparotomy is a staging laparoscopy to identify peritoneal or liver metastases. However, pre-operative cross-sectional imaging resolution have also steadily improved, and routine staging laparoscopy is still controversial.[8] Nonetheless, a subset of patients with a high-risk for occult metastatic disease might potentially benefit from staging laparoscopy. The National Comprehensive Cancer Network (NCCN) guidelines define patients with borderline resectable disease, markedly elevated serum CA19-9 levels, large primary tumors or large regional lymph nodes as high-risk for occult metastases.[8] The guideline advises to consider a staging laparoscopy in those patients. However, cutoff values or a risk model to assist decision making whether to perform a staging laparoscopy are not available and the use of a staging laparoscopy differs between hospitals.

This study aimed to develop and externally validate a preoperative prediction model for occult distant metastases in patients with presumed (borderline) resectable pancreatic cancer.

METHODS

This study was performed in accordance with the TRIPOD guidelines for the development and validation of multivariable prediction models.[9] Data from the Dutch Pancreatic Cancer Audit (DPCA) were used and a scientific committee governing these data reviewed the study proposal.[10] This prospective registry monitoring quality of care is

mandatory for all 18 Dutch centers performing pancreatic surgery and has demonstrated over 90% case ascertainment and over 95% data accuracy.[11] Since the data provided to the study team were anonymized, the need for informed consent was waived.

Study population

For the development cohort, all patients with a suspected pancreatic malignancy, who underwent surgery with intent for resection between January 2013 and December 2017 in the Netherlands, were included from the DPCA. Patients with neuroendocrine tumors were excluded as well as patients younger than 18 years, patients with MDCT imaging more than 6 weeks before surgery, and patients with missing data regarding pre-operative imaging or primary outcome. Because neoadjuvant treatment was given sporadically, within a clinical trial with a protocolled staging laparoscopy before the start of neoadjuvant therapy, these patients were excluded.[12] Standard workup for suspected pancreatic cancer included a minimum of a MDCT with a 3-mm slice-interval according to a biphasic protocol consisting of an arterial phase and a portal phase (35-40 and 60-70 seconds after intravenous contrast injection respectively).[13] Magnetic resonance imaging (MRI) and/or positron-emission tomography computed tomography (PET-CT) were performed on individual basis and according to local preferences after a consensus meeting of the multidisciplinary team. The choice of a staging laparoscopy before explorative laparotomy was at the discretion of the surgeon.

External validation was performed in a prospectively maintained institutional database from a high-volume pancreatic center: University of Verona Hospital Trust (Verona, Italy; cohort 2013 – 2017). This cohort included all consecutive treatment-naive patients with a pancreatic ductal adenocarcinoma undergoing an exploratory laparotomy or laparoscopy with intent for resection. Similar to the developmental cohort, the standard preoperative workup always included a 3mm-sliced MDCT using a tri-phasic pancreatic protocol. In patients deemed to be at high risk for distant metastases (e.g., elevated Ca 19.9 levels, suspicious lesions on MDCT) MRI, PET-CT and/or staging laparoscopy were recommended by the multidisciplinary team. Only patients with available MDCT imaging within 6 weeks before surgery were included. Data were extracted from the institutional database after anonymization and used in compliance with the Institutional Review Board approval for retrospective protocols (PAD-R 1101CESC).

Definitions, outcome, and predictors

The primary outcome was defined as pathologically proven liver, peritoneal or omental metastases during exploratory laparotomy or staging laparoscopy. Potential predictor variables were selected based on a literature search and clinical reasoning. Clinical predictor variables included: age, sex, body mass index (BMI), comorbidity, Eastern

Cooperative Oncology Group (ECOG) performance status at diagnosis (class 0, 1, and ≥2), weight loss, pre-operative nutritional support with tube feeding or total parenteral nutrition, serum CA19-9 levels (highest baseline during pre-operative period in kU/L), and biliary drainage. Candidate radiographic predictors were: tumor location (uncinated process/head, body/tail), biggest tumor diameter, tumor composition (i.e. predominantly solid versus cystic), suspicion of regional lymph node metastases, vascular involvement, T-stage≥T3 (according to American Joint Committee on Cancer TNM classification, 7th edition[14]) and indeterminate lesions on computed tomography (CT) scan and/or MRI. Regional lymph nodes were scored as suspected when above 10mm diameter.[15] Indeterminate lesions were defined as subcentimetric or aspecific liver or peritoneal lesions on imaging, which could not be definitively characterized or excluded as metastases with further work-up. Other covariables taken into consideration were time from first presentation to surgery and time from MDCT to surgery.

Model development and data analysis

Data were presented as mean with standard deviation (SD), or median with interquartile range when appropriate for continuous data and counts with percentage for categorical data. Expecting an event rate of at least 8% and using the '1 to 10 rule of thumb', a sample size of at least 2250 patients would have been needed to achieve a stable prediction model with 18 candidate predictors[7,16] Missing data were imputed using multiple imputation (Multiple Imputation by Chained Equations, 20 imputed datasets with a maximum number of 5 iterations for each imputation).[17,18] Continuous variables were log transformed and systematically tested to explore non-linearity with primary outcome. Only tumor size turned out to perform better when transformed. In each imputed dataset, the full multivariable logistic regression model including the variables as described, with occult metastases as outcome variable was fitted. Subsequently, stepwise backward selection based on the Akaike Information Criterion was used to select relevant variables.[19] This resulted in 20 sets of variables being selected in the 20 imputed sets based on the Akaike Information Criterion. Variable selection for the multivariable logistic regression model took place using the majority rule, that is the variable was retained within the model when the variable was appearing in at least 50% of the imputation sets.[20] Further stepwise backward selection was based on the likelihood ratio test. The final multivariable logistic regression model was fitted with these selected predictors in each imputation set, and model coefficients were pooled using Rubin's rules.[21] The discriminatory ability of the model was evaluated by the area under the receiver operating characteristic (ROC) curve in the development set and the external validation set, resulting in the C-statistic. Model calibration of the final model was evaluated by visual inspection of the model calibration plot.

All statistical analyses were performed using R 3.1.2 open-source software ('mice', 'MASS', 'pROC' and 'rms' packages, http://www.R-project.org). A p-value of <0.05 was considered statistically significant.

RESULTS

In total, 2925 patients who underwent an exploratory laparotomy or laparoscopy with the intention for pancreatic resection were included for model design and external validation. Baseline characteristics are given in Table 1. Within the development cohort (n=2262), the mean age was 66 years (SD ±10), 88% (n=1836) had an ECOG performance score of 0-1, the median pre-operative serum CA19-9 was 110 kU/L (IQR 20 – 490). Tumors were mostly located in the pancreatic head or uncinate process (n=1251, 81%). 3% (n=57) of patients had indeterminate lesions on imaging, that could not be characterized or excluded as metastases with further work-up. In total, 10% (n=235) of patients were diagnosed with occult distant metastases. In patients undergoing staging laparoscopy (n=282, 13%), laparoscopy was done in the same session as the exploratory laparotomy with intention for resection in 84% of cases (n=175). With staging laparoscopy, 42 of 60 (70%) occult metastases were detected. The remaining 18 were located in liver (n=9, 50%), peritoneum (n=7, 39%) or both (n=2, 11%) and were found during exploratory laparotomy. The majority of occult distant metastases was found during exploratory laparotomy not preceded by staging laparoscopy (n=175, 74% of patients with occult metastases). Most metastases were located in the liver (n=143, 61%), followed by peritoneal lesions (n=73, 31%) or both (n=19, 8%) (Table 2).

Baseline characteristics of the validation cohort (n=663) are shown in Table 1. The incidence of occult metastases was 9% (n=60), with 65% (n=39) located in the liver, 25% (n=15) located peritoneal, and 10% (n=6) located in both (Table 2).

Model development and performance

Univariable analyses identified age, ECOG PS, weight loss, pre-operative nutritional support, CA19-9, tumor diameter, a cystic tumor composition, vascular involvement, ≥T3 tumor, indeterminate lesions on imaging, and the number of weeks from the first consultation to surgery as variables that were significantly associated with occult metastases (Table 3).

Table 1. Baseline characteristics

	Development cohort n=2262	Missing values n (%)	Validation cohort n=663	Missing values n (%)
Age, years (SD)	66 (10)	37 (2)	66 (10)	0 (0)
Male sex, n(%)	1213 (54)	32 (1)	361 (54)	0 (0)
BMI, kg/m^2 (SD)	25.1 (4.3)	101 (5)	24.3 (3.7)	51 (8)
Comorbidity (any), n(%)	1798 (80)	11 (1)	353 (53)	9 (1)
ECOG performance status, n(%)		186 (8)	NA	NA
0	972 (47)			
1	864 (42)			
≥2	240 (12)			
Weight loss, n(%)	1418 (74)	346 (15)	306 (46)	11 (2)
Preoperative biliary drainage, n(%)	956 (44)	102 (5)	304 (46)	0 (0)
Nutritional support, n(%)	157 (7)	88 (4)	4 (1)	6 (1)
CA19-9, kU/l (IQR)	110 (20 – 490)	1003 (44)	102 (29 – 367)	143 (22)
Tumor location, n(%)		715 (32)		0 (0)
Head/uncinate process	1251 (81)		494 (75)	
Body/tail	296 (19)		169 (25)	
Tumor diameter, mm (IQR)	28 (21 – 37)	808 (36)	25 (20 – 34)	60 (9)
Cystic tumor composition, n(%)	230 (10)	47 (2)	99 (15)	27 (4)
Lymph node metastases, n(%)	322 (15)	105 (5)	NA	NA
Vascular involvement, n(%)	765 (35)	90 (4)	55 (8)	2 (0.3)
≥T3 tumor (TNM 7th edition), n(%)	332 (15)	106 (5)	NA	NA
Type of imaging, n(%)		0 (0)	NA	NA
CT-scan only	1652 (73)			
MRI/MRCP only	68 (3)			
CT-scan and MRI/MRCP	542 (24)			
Indeterminate lesions[a], n(%)	57 (3)	66 (3)	26 (4)	27 (4)
Weeks from CT-scan to surgery, n (%)		129 (6)	NA	NA
0-2	583 (27)			
2-4	840 (39)			
4-6	710 (33)			
Weeks from 1st consult to surgery (IQR)	4 (2 – 5)	75 (3)	6 (3 – 8)	181 (27)
DLS before exploration, n(%)	282 (13)	25 (1)	NA	NA

[a] Subcentimeter or aspecific lesions on imaging, which could not be definitively characterized or excluded as metastases with further work-up. Abbreviations: BMI, body mass index; MRI, magnetic resonance imaging; DLS, diagnostic laparoscopy; SD, standard deviation; IQR, interquartile range; NA, data not available from validation cohort

The final multivariable model included the following predictors of distant metastases during exploratory surgery (Table 4): higher age (OR 1.02, 95%CI 1.00-1.03), lower BMI (OR 0.96, 95%CI 0.93-0.99), preoperative nutritional support (OR 1.73 95%CI 1.010-2.74), larger tumor diameter (OR 1.60, 95%CI 1.04-2.45), solid tumor composition (versus cystic; OR 2.33, 95%CI 1.20-4.35), indeterminate liver or peritoneal lesions on imaging (OR 4.01, 95%CI 2.16-7.43).

The model had a moderate discriminatory ability in the development cohort with a C-statistic of 0.65. External validation, using the Verona data cohort, demonstrated a poor discriminatory ability with a C-statistic of 0.56, and a poor calibration upon visual inspection (Figure 1).

Table 2. Occult metastases

	Development cohort (DPCA data) n=235	**Validation cohort (Verona data) n=60**
Location, n (%)		
Liver only	143 (61)	39 (65)
Peritoneal only	73 (31)	15 (25)
Liver + peritoneal	19 (8)	6 (10)
Diagnosed with laparoscopy only	42 (18)	NA

Abbreviations: DPCA, Dutch Pancreatic Cancer Audit; NA, data not available

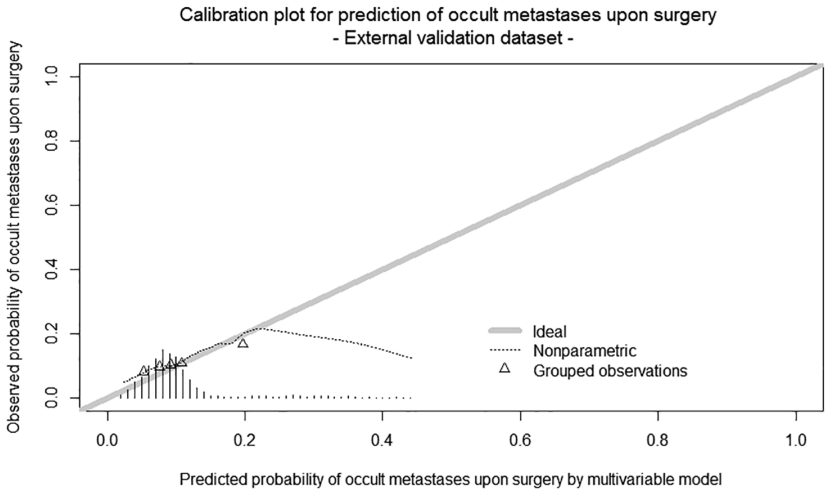


Figure 1. Calibration plot of external validation (Verona data)

Table 3. Univariable analysis: predictors for occult metastases in development cohort (DPCA data)

	No occult metastases n=2027	Occult metastases n=235	p-value
Age, years (SD)	66 (10)	68 (10)	**0.014**
Male sex, n(%)	1084 (54)	129 (56)	0.635
BMI, kg/m^2 (SD)	25.1 (4.3)	24.6 (4.2)	0.082
Comorbidity (any), n(%)	1608 (80)	190 (81)	0.758
ECOG performance status, n(%)			**0.028**
0	888 (48)	84 (38)	
1	757 (41)	107 (49)	
≥2	212 (11)	28 (13)	
Weight loss, n(%)	1255 (73)	163 (84)	**0.002**
Preoperative biliary drainage, n(%)	842 (44)	114 (50)	0.066
Nutritional support, n(%)	128 (7)	29 (13)	**0.001**
CA19-9, kU/l (IQR)	103 (20 – 462)	206 (29 – 796)	**0.016**
Tumor location, n(%)			1.000
Head/uncinate process	1118 (81)	133 (81)	
Body/tail	264 (19)	32 (19)	
Tumor diameter, mm (IQR)	28 (21 – 36)	30 (25 – 40)	**<0.001**
Cystic tumor composition, n(%)	219 (11)	11 (5)	**0.005**
Lymph node metastases, n(%)	282 (15)	40 (18)	0.230
Vascular involvement, n(%)	672 (35)	93 (42)	**0.034**
≥T3 tumor (TNM 7th edition), n(%)	284 (15)	48 (22)	**0.008**
Indeterminate lesions[a], n(%)	40 (2)	17 (7.4)	**<0.001**
Weeks from CT-scan to surgery, n(%)			0.959
0-2	522 (27)	61 (27)	
2-4	749 (39)	91 (40)	
4-6	636 (33)	74 (33)	
Weeks from 1st consult to surgery (IQR)	3 (2 – 5)	3 (2 – 5)	0.009

a Subcentimeter or aspecific lesions on imaging, which could not be definitively characterized or excluded as metastases with further work-up. Abbreviations: BMI, body mass index; SD, standard deviation; IQR, interquartile range.

Table 4. Multivariable analysis of predictors for occult metastases in DPCA cohort

Variables	β coefficient	OR (95%CI)	p-value
Intercept	-4.009		
Age	0.018	1.018 (1.003-1.034)	0.02
BMI	-0.039	0.961 (0.926-0.998)	0.04
Nutritional support	0.549	1.732 (1.096-2.737)	0.02
Cystic tumor composition (versus solid)	-0.834	0.434 (0.227-0.831)	0.01
Tumor diameter (log)	0.468	1.596 (1.038-2.453)	0.04
Indeterminate lesions on imaging[a]	1.387	4.005 (2.158-7.432)	<0.001

Abbreviations: DPCA, Dutch Pancreatic Cancer Audit; TPN, total parenteral nutrition.
[a] Subcentimeter or aspecific lesions on imaging, which could not be definitively characterized or excluded as metastases with further work-up.

DISCUSSION

In this study, 10% of patients with presumed resectable and borderline resectable pancreatic cancer had occult metastases during exploratory laparotomy or laparoscopy. Higher age, lower BMI, preoperative nutritional support, a solid tumor composition (versus cystic), a larger tumor diameter and indeterminate lesions on preoperative imaging were identified as predictors for the presence of occult metastases during surgery. Although these predictor variables were significantly associated with occult metastases, the discrimination ability of the prediction model was insufficient after external validation within the Verona dataset.

The most frequent identified predictors from other studies that performed multivariable analyses to predict occult metastases are serum CA19-9 and tumor size.[7,22–29] In addition, age, sex, vascular involvement, lymph node involvement, tumor location, indeterminate (liver) lesions on imaging and time to surgery have also been previously described as predictors, although less often.[7,22–24,26–28,30] While nutritional support and BMI have not been studied before in relation to the presence of occult metastases, previous studies did report (back) pain, jaundice and weight loss as potential predictors for occult metastases.[7,29,31] Not only are these factors indicators for a worse physical condition, a lower BMI or nutritional support and thereby lower visceral adipose tissue can also impede the evaluation of staging CT scans leading to a higher risk of missing suspicious lesions.[32]

Concerning the radiological composition of the tumor, it is known that adenocarcinomas deriving from cystic intraductal papillary mucinous neoplasms (IPMNs) have a better overall survival and relatively indolent behavior when compared to adenocarcinoma

with pancreatic intraepithelial neoplasms (PanINs) as precursor lesion.[33] This can be an explanation for the lower incidence of occult metastases when a suspected malignant lesion had a cystic component on CT imaging in the current study.

A consensus document from the Americas Hepato-Pancreato-Biliary Association includes equivocal findings on imaging, together with a tumor size above 3 cm, CA19-9 above 100 kU/L and body/tail lesions as predictors on the basis upon which patients should be selected for staging laparoscopy.[30] Other studies argue that only CA19-9 and tumor size are reliable surrogate markers for selecting patients for staging laparoscopy and the NCCN guidelines include vascular involvement, serum CA19-[9], tumor size, lymph node size and excessive pain or weight loss as guide to perform a staging laparoscopy.[8,34] This lack of consensus can be attributed to the lack of evidence, with no solid external validation from previously published models.
External validation of the model developed in the current study demonstrated that the available variables in the current dataset where not sufficient to develop a robust predictive model. An explanation for the disappointing discrimination and calibration within the Verona dataset might have been the case mix and possible differences in pre-operative management between the two centers.[35] For example, patients from the Verona cohort less frequently received nutritional support compared to the DPCA cohort (Table 1). Moreover, patients with vascular involvement often received neoadjuvant treatment within the Verona cohort, and those were excluded from the current analysis. Prediction models in pancreatic cancer have been known for disappointing discrimination ability so, the currently available pre-operative patient and tumor characteristics appear not sufficient enough to predict outcomes in this multifactorial disease. Tumor biology is difficult to measure and especially for pancreatic cancer, until now, clinically useful biomarkers are lacking, and new biomarkers are extensively studied. For example circulating tumor cells or tumor DNA or RNA could be of use when predicting occult metastases and should be included in future models besides pre-operative patient and tumor characteristics.[36] A recent pilot study described a phenotype circulating tumor cell (CTC)-based blood test with a 100% sensitivity and 89% specificity for metastases in pancreatic cancer. Although the sample size was small and the test needs an appropriate device to harvest CTCs, these results can be regarded as promising.[37]

Although the current study cannot yet resolve the controversial role of staging laparoscopy, this study showed that three quarters of patients with occult metastases were diagnosed during a primary explorative laparotomy. Giving the high impact of a laparotomy when compared to a laparoscopy, it seems that a staging laparoscopy should be performed with lower thresholds. Some centers already perform a routine

staging laparoscopy at the start of every pancreatic surgical procedure. Not only could it prevent the morbidity and possible delay in systemic treatment that accompanies an unnecessary laparotomy in a patient's final stage of life.[30] Other studies showed that 10% - 20% of unnecessary laparotomies could be avoided when preceded by a staging laparoscopy.[24,27,38] Within the current era of emerging neoadjuvant therapies, the percentage of futile laparotomies might be lower since occult metastases might become unmeasurable with laparoscopy after chemotherapy. Therefore, future studies should also include patients treated with neoadjuvant therapy. Furthermore, with enhancing technologies, it is likely that the preoperative risk assessment could be improved with for example, improved DWI sequences and hepatobiliary contrast series during magnetic resonance investigation (MRI) or alternative tracers in (PET-) CT imaging.[39–41]

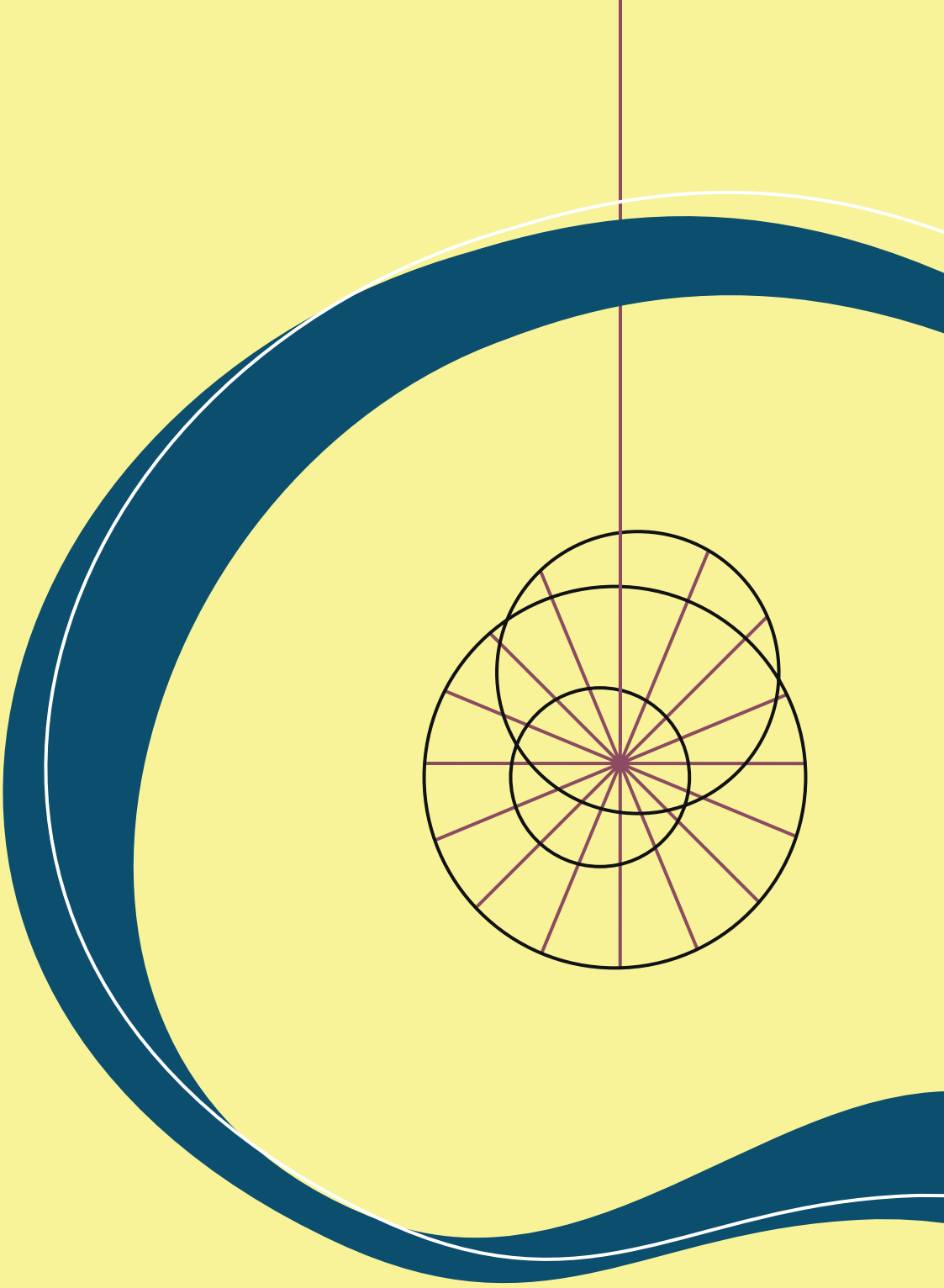
Some aspects of the study should be interpreted with care. First, the dataset did not include details on vascular involvement. A study of Satoi *et al.* and others have showed that involvement of the portal vein was significantly associated with surgical unresectability, mainly based on the presence of occult metastases.[27] Second, serum CA19-9 had a high percentage of missing data. Nevertheless, imputing up to 50% of missing data is generally accepted, provided that data are missing at random.[42] Strengths of this study include the sample size, extent, and multicenter character of the DPCA dataset, which allowed a proper statistical analysis. Moreover, this study was the first to attempt a broad validation of a predictive model for occult metastases in patients with pancreatic cancer.

In conclusion, based on this study we were not able to accurately predict occult metastases in patients with presumed resectable and borderline resectable pancreatic cancer. The need for preoperative nutritional support, low BMI, larger tumor size, solid tumor components, higher age and indeterminate lesions on pre-operative imaging were associated with occult metastases upon surgery. A staging laparoscopy should be considered more often since in this study the majority of occult metastases was found during primary laparotomy. Future studies should focus on biological markers in addition to the currently available pre-operative clinical and radiological parameters to improve the prediction of occult metastases. Until then, performing a laparoscopy will remain mainly a surgeon's choice.

REFERENCES

1. Rahib, L. *et al.* Projecting cancer incidence and deaths to 2030: The unexpected burden of thyroid, liver, and pancreas cancers in the united states. *Cancer Res.* **74**, 2913–2921 (2014).
2. Bray, F. *et al.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA. Cancer J. Clin.* **68**, 394–424 (2018).
3. Vincent, A., Herman, J., Schulick, R., Hruban, R. H. & Goggins, M. Pancreatic cancer. *Lancet* **378**, 607–620 (2011).
4. Latenstein, A. E. J. *et al*. Nationwide trends in incidence, treatment and survival of pancreatic ductal adenocarcinoma. Eur. J. Cancer 125, 83–83 (2020).
5. Kamisawa, T., Wood, L. D., Itoi, T. & Takaori, K. Pancreatic cancer. Lancet 388, 73–85 (2016).
6. van der Geest, L. G. M. *et al.* Nationwide outcomes in patients undergoing surgical exploration without resection for pancreatic cancer. Br. J. Surg. 104, 1568–1577 (2017).
7. Gemenetzis, G. *et al*. Incidence and risk factors for abdominal occult metastatic disease in patients with pancreatic adenocarcinoma. J. Surg. Oncol. 118, 1277–1284 (2018).
8. Tempero, M. A. *et al*. Pancreatic adenocarcinoma, version 2.2017: Clinical practice guidelines in Oncology. JNCCN Journal of the National Comprehensive Cancer Network vol. 15 1028–1061 (2017).
9. Moons, K. G. M. *et al*. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): Explanation and elaboration. Ann. Intern. Med. 162, W1–W73 (2015).
10. Strijker, M. *et al*. Establishing and Coordinating a Nationwide Multidisciplinary Study Group: Lessons Learned by the Dutch Pancreatic Cancer Group. Ann. Surg. 271, e102–e104 (2020).
11. van Rijssen, L. B. *et al*. Nationwide prospective audit of pancreatic surgery: design, accuracy, and outcomes of the Dutch Pancreatic Cancer Audit. HPB 19, 919–926 (2017).
12. Versteijne, E. *et al*. Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Results of the Dutch Randomized Phase III PREOPANC Trial. J. Clin. Oncol. (2020) doi:10.1200/JCO.19.02274.
13. IKNL- The Netherlands Cancer Registry. Dutch guidelines pancreatic cancer. Version 2.0. https://www.oncoline.nl/pancreascarcinoom (2011).
14. AJCC. AJCC Cancer Staging Manual. https://cancerstaging.org/references-tools/deskreferences/Pages/default.aspx (2009).
15. Einstein, D. M., Singer, A. A., Chilcote, W. A. & Desai, R. K. Abdominal lymphadenopathy: spectrum of CT findings. RadioGraphics 11, 457–472 (2013).
16. P., P., J., C., E., K., T.R., H. & A.R., F. A simulation study of the number of events per variable in logistic regression analysis. J. Clin. Epidemiol. 49, 1373–1379 (1996).
17. Sterne, J. A. C. *et al*. Multiple imputation for missing data in epidemiological and clinical research: Potential and pitfalls. BMJ (Online) vol. 339 157–160 (2009).
18. White, I. R., Royston, P. & Wood, A. M. Multiple imputation using chained equations: Issues and guidance for practice. Stat. Med. 30, 377–399 (2011).
19. Posada, D. & Buckley, T. R. Model selection and model averaging in phylogenetics: Advantages of akaike information criterion and bayesian approaches over likelihood ratio tests. Systematic Biology vol. 53 793–808 (2004).
20. Wood, A. M., White, I. R. & Royston, P. How should variable selection be performed with multiply imputed data? Stat. Med. 27, 3227–3246 (2008).
21. Rubin, D. B. Multiple imputation for nonresponse in surveys Donald B. Rubin. Wiley Series in Probability and Statistics (1987). doi:10.1002/9780470316696.
22. Liu, X. *et al*. Predictors of distant metastasis on exploration in patients with potentially resectable pancreatic cancer. BMC Gastroenterol. 18, 168 (2018).
23. Fong, Z. V. *et al*. Reappraisal of Staging Laparoscopy for Patients with Pancreatic Adenocarcinoma: A Contemporary Analysis of 1001 Patients. Ann. Surg. Oncol. 24, 3203–3211 (2017).
24. Karachristos, A., Scarmeas, N. & Hoffman, J. P. CA 19-9 levels predict results of staging laparoscopy in pancreatic cancer. J. Gastrointest. Surg. 9, 1286–1292 (2005).
25. Oba, A. *et al*. Radiologically occult metastatic pancreatic cancer: how can we avoid unbeneficial resection? Langenbeck's Arch. Surg. (2020) doi:10.1007/s00423-019-01846-2.

26. Lee, H. S. *et al*. Preoperative prediction of futile surgery in patients with radiologically resectable or borderline resectable pancreatic adenocarcinoma. J. Gastroenterol. Hepatol. (2020) doi:10.1111/jgh.14837.
27. Satoi, S. *et al*. Selective Use of Staging Laparoscopy Based on Carbohydrate Antigen 19-9 Level and Tumor Size in Patients With Radiographically Defined Potentially or Borderline Resectable Pancreatic Cancer. Pancreas 40, 426–432 (2011).
28. Gerken, K. *et al*. Development and multicentre validation of a prognostic model to predict resectability of pancreatic head malignancy. BJS open 2, 319–327 (2018).
29. Slaar, A. *et al*. Predicting distant metastasis in patients with suspected pancreatic and periampullary tumors for selective use of staging laparoscopy. World J. Surg. (2011) doi:10.1007/s00268-011-1204-6.
30. Callery, M. P. *et al*. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: Expert consensus statement. in Annals of Surgical Oncology (2009). doi:10.1245/s10434-009-0408-6.
31. Gerken, K. *et al*. Development and multicentre validation of a prognostic model to predict resectability of pancreatic head malignancy. BJS Open (2018) doi:10.1002/bjs5.79.
32. Liu, L. H., Zhou, G. F., Zhou, J. J., Rao, S. X. & Zeng, M. S. Impact of visceral adipose tissue on the accuracy of T-staging by CT in colon cancer. Eur. J. Radiol. (2021) doi:10.1016/j.ejrad.2020.109400.
33. McGinnis, T. *et al*. Survival outcomes of pancreatic intraepithelial neoplasm (PanIN) versus intraductal papillary mucinous neoplasm (IPMN) associated pancreatic adenocarcinoma. J. Clin. Oncol. (2020) doi:10.1200/jco.2020.38.4_suppl.766.
34. De Rosa, A., Cameron, I. C. & Gomez, D. Indications for staging laparoscopy in pancreatic cancer. HPB (2016) doi:10.1016/j.hpb.2015.10.004.
35. Pencina, M. J. & D'Agostino, R. B. Evaluating discrimination of risk prediction models: The C statistic. JAMA - Journal of the American Medical Association (2015) doi:10.1001/jama.2015.11082.
36. Court, C. M. *et al*. Circulating Tumor Cells Predict Occult Metastatic Disease and Prognosis in Pancreatic Cancer. Ann. Surg. Oncol. 25, 1000–1008 (2018).
37. Sun, Y. *et al*. CTC phenotyping for a preoperative assessment of tumor metastasis and overall survival of pancreatic ductal adenocarcinoma patients. EBioMedicine (2019) doi:10.1016/j.ebiom.2019.07.044.
38. Allen, V. B., Gurusamy, K. S., Takwoingi, Y., Kalia, A. & Davidson, B. R. Diagnostic accuracy of laparoscopy following computed tomography (CT) scanning for assessing the resectability with curative intent in pancreatic and periampullary cancer. Cochrane Database of Systematic Reviews (2016) doi:10.1002/14651858.CD009323.pub3.
39. Marion-Audibert, A.-M. *et al*. Routine MRI With DWI Sequences to Detect Liver Metastases in Patients With Potentially Resectable Pancreatic Ductal Carcinoma and Normal Liver CT: A Prospective Multicenter Study. AJR. Am. J. Roentgenol. 211, W217–W225 (2018).
40. Ito, T. *et al*. The diagnostic advantage of EOB-MR imaging over CT in the detection of liver metastasis in patients with potentially resectable pancreatic cancer. Pancreatology 17, 451–456 (2017).
41. Kim, H. W. *et al*. Adjunctive role of preoperative liver magnetic resonance imaging for potentially resectable pancreatic cancer. Surgery 161, 1579–1587 (2017).
42. Madley-Dowd, P., Hughes, R., Tilling, K. & Heron, J. The proportion of missing data should not be used to guide decisions on multiple imputation. J. Clin. Epidemiol. (2019) doi:10.1016/j.jclinepi.2019.02.016.



PART III
Local ablative therapies

Chapter 8

Eligibility criteria for radiofrequency ablation and irreversible electroporation in locally advanced, unresectable pancreatic cancer: an overview of literature and retrospective cohort study

Submitted

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ABSTRACT

Background

Radiofrequency ablation (RFA) and irreversible electroporation (IRE) are experimental treatment modalities for locally advanced, unresectable pancreatic cancer (LAPC) that are increasingly used. It remains unclear whether IRE and RFA are competitive or complementary therapies. This study aims to summarize eligibility criteria for irreversible electroporation (IRE) and radiofrequency ablation (RFA) and to assess the extent of overlap or exclusiveness in eligibility for RFA and IRE in patients with LAPC.

Methods

An overview of literature was given in order to summarize eligibility criteria for RFA and IRE. Patients diagnosed with LAPC from a previously described cohort (IMPALA study) were included. An interventional radiologist assessed the eligibility for RFA and IRE, based on a CT-scan after at least 2 months of chemotherapy. Tumor characteristics of groups eligible for RFA only, eligible for IRE only or eligible for both were compared.

Results

In total, 58 patients with LAPC were included. When using eligibility criteria based upon 31 published studies, 53 (91%) patients were eligible for either RFA or IRE. Of these, 36 patients (62%) were eligible for RFA and 44 (76%) for IRE. 26 patients (45%) were eligible for only one of both. When comparing patients eligible for RFA only (n=9, 16%), IRE only (n=17, 29%) or eligible for both (n=27, 47%), tumor diameter (58mm±8mm vs. 33mm±15mm vs. 43mm±12mm;$p<0.001$) and tumor location (67%, n=6 vs. 19%, n=5 vs. 35%, n=6 body/tail tumors; p=0.026) were significantly different.

Conclusion

In this study, the vast majority of patients with LAPC is eligible for at least one ablative treatment strategy. IRE and RFA are equally competitive (47% of cases) as they are complementary (45% of cases). This stresses the need for randomized clinical trials on efficacy of both ablative therapies.

INTRODUCTION

In patients with locally advanced, unresectable pancreatic cancer (LAPC) a surgical resection is impossible due to extensive vascular tumor involvement, without distant metastases. Unfortunately, treatment options for these patients are mainly palliative and associated with a poor clinical outcome.[1-3] Because overall survival remains disappointing, new treatment strategies for these patients can be of great potential. Although randomized controlled trials (RCTs) are still lacking, a systematic review of non-randomized studies suggested a survival benefit of local ablation strategies in patients with LAPC.[4] At the moment, this causes a rapid and important expansion of the use of local ablative therapies in the experimental setting in patients with LAPC.

Two ablation strategies, of which efficacy and safety are currently being studied in RCTs, are radiofrequency ablation (RFA) and irreversible electroporation (IRE).[5,6] RFA is an energy-based technique aiming for partial tumor ablation by frictional heating. It has recently been shown that RFA induces an immune response different from normal surgical stress.[7] It is hypothesized that besides the debulking effect, this can result in an abscopal effect that can improve overall survival.[8] IRE is considered a non-thermal technique that applies high voltage electrical pulses between electrodes leading to apoptosis of tumor cells without damaging adjacent vascular structures and aims to achieve complete tumor ablation.[9]

During RFA in patients with LAPC, a non-ablated safety margin to adjacent vital structures has to be maintained to avoid thermal damage, suggesting this technique requires a rather 'bulky' tumor.[10] In contrast, tumor size might limit the applicability of IRE, since IRE electrodes have a maximum spacing distance and the procedure lengthens and gets more complicated with more electrodes.[11,12] This suggests that a different spectrum of tumors are eligible for RFA versus IRE and treatment strategies might be complementary rather than competitive. However, the literature so far does not offer a lot of guidance regarding the choice of ablative therapy and focus on one treatment strategy rather than comparing both. Moreover, most studies only report on the outcomes of patients who were considered eligible for local ablative treatment prior to study inclusion, without reporting on the prior selection process of the in-and excluded patients. Therefore it is currently unclear in which patients RFA and IRE is truly applicable and to what extent both modalities are complementary or competitive.

The current study aims to 1) define eligibility criteria for IRE and RFA from current available literature and 2) assess the extent of overlap or exclusiveness in eligibility for RFA and IRE, within a previous published cohort of consecutive patients with LAPC.

METHODS

Study population

Patients diagnosed with LAPC between September 2013 and March 2015 from a previously described prospectively registered cohort[13] with non-progressive disease after at least 2 months of chemotherapy, were included. This previous study (IMPALA), was approved by the institutional ethical committee and registered at the Netherlands Trial Registry (NTR4230). Written informed consent was obtained for patients included in the IMPALA study.

LAPC was determined during a multidisciplinary team meeting, according to the consensus criteria of the Dutch Pancreatic Cancer Group (DPCG).[14] Restaging during chemotherapy was performed with a thoracic and abdominal computed tomography (CT) scan according to a biphasic protocol consisting of a late arterial phase and a late portal phase (35-40 and 60-70 seconds after intravenous contrast injection respectively). In 10 cases, only a monophasic portal venous scan was available with a post threshold delay of 65-70 seconds. The images were acquired in craniocaudal direction, with 2mm and 3mm slice thickness for the arterial and portal venous phase respectively, 0.6mm increment, 120kV and 140mAs. Reconstructions were made with a 2mm thickness and increment for the arterial and 3mm thickness and increment for the portal venous phase. Non-progressive disease was defined in accordance with the Response Evaluation Criteria In Solid Tumors (RECIST version 1.1)[15] and was scored by an abdominal radiologist within the multidisciplinary team meeting.

Treatment eligibility

In order to define eligibility criteria for RFA and IRE the PubMed database was searched for previously published studies on pancreatic RFA and IRE procedures until 6th December 2017. Additional studies were identified through a reference check from review and key articles. Original articles, animal studies and review articles specifically aiming on technique description were included. IRE studies for margin accentuation during surgery, case reports (n<5), conference abstracts and articles from the same authors or research group without new data were excluded. A full description of the search strategy and an overview of extracted data are available in Additional files 1-3.

All CT-scans were systematically assessed for eligibility for IRE and for RFA therapy, by an interventional radiologist with 20 years of experience in RFA and 5 years of experience in IRE. The assumption was made that the multipolar CelonLab® POWER System generator with CelonPro*Surge*® and CelonPro*Surge*® *micro* probes would be used for RFA during laparotomy (Olympus Surgical Technologies Europe, Teltow, Germany). Exposure length

of available RFA electrodes range from 9-40mm with a 8-20mm diameter ablation zone. For intra-operative IRE, the Nanoknife® system (AngioDynamics, Amsterdam, the Netherlands) was used with a maximum electrode exposure length of 15mm.

Statistics

Statistical analysis was performed with SPSS version 22.0 (SPSS Inc., Chicago, Illinios, USA). Patient characteristics and study outcomes were presented with descriptive statistics using mean with standard deviation, median with interquartile range or number with percentage when appropriate. A proportional Venn diagram was created using R statistical software version 3.1.1 (http://R-project.org). Differences between groups were tested using the one-way between groups ANOVA and chi-square test. A value of $P < 0.05$ was used as level of significance.

RESULTS

Study population

In total, 58 out of 59 patients with non-progressive disease had a restaging CT-scan available for review and were enrolled in this study. Baseline and tumor characteristics are summarized in Table 1.

Overview of literature

Overall, 31 studies were included. Twelve described RFA procedures and 19 IRE (see Additional files 2-3). Within four RFA and three IRE studies, patients with metastases were included, but without a survival benefit.[16-22] The majority of studies included patients after primary treatment with chemo- or (chemo)radiotherapy, since Girelli *et al.*[23] showed this can select the patients who would not benefit from RFA.[10,11,20-22,24-35] All procedures were performed during general anesthesia except for one study performing percutaneous RFA under deep sedation.[36] A summary of general eligibility criteria for ablative therapies based on available literature is shown in Table 2.

Eligibility criteria RFA

Most studies agreed that ablation temperature should not exceed 90°C, since this doubled the risk of portomesenteric thrombosis, duodenal ulcers and bleeding.[23] Seven articles described a minimal safety distance from the RFA electrode to vital structures ranging from 5-15mm, with ablation zone diameters ranging from 10-65mm (see Additional file 2).[10,18,32,36-39] One study concluded that a 5mm distance from the RFA electrode to vital structures might not be sufficient since a 25% mortality rate was observed (ablation diameter not reported).[18] One animal study assessed histopathology

after ablation and temperature measurement at several distances. In this study a distance of 5 and 0mm from the edge of the ablation zone (i.e. 15 and 10mm from the electrode) to the portomesenteric vein (PMV) and duodenum respectively was considered as safe when the duodenum was perfused with cold saline through nasogastric tubes.[37] Less specific but often described, is that the ablation area should not exceed the tumor area to ensure a non-defined margin to contiguous vascular and digestive structures.[10,19,23,36] Based on these results, the eligibility criteria for RFA as shown in Table 2 were established.

Table 1. Baseline characteristics

Characteristic	All patients (n = 58)
Age, years (SD)	61 (11)
Male sex, n (%)	31 (53)
WHO score, n (%)[a]	
0	37 (64)
1	14 (24)
2	3 (5)
Comorbidity, n (%)	
Cardiopulmonary	10 (17)
Vascular	14 (24)
Other[b]	23 (40)
None	29 (50)
Tumor location, n (%)	
Head/uncinate process	39 (67)
Body/tail	19 (33)
Tumor diameter, mm (SD)[c]	42 (15)
First line chemotherapy regimen, n (%)	
FOLFIRINOX	42 (72)
Gemcitabine monotherapy	10 (17)
Gemcitabine combination therapy	3 (5)
Chemoradiation	2 (3)
CAPOX	1 (2)
Resection after restaging, n (%)	14 (24)

SD, standard deviation; CAPOX, capecitabine and oxaliplatin

[a] missing cases n = 4; [b] does not affect IRE/RFA eligibility (i.e. previous malignancy, psychiatric, endocrine, auto-immune, hematologic, musculoskeletal, mild renal insufficiency); [c] from 3 patients, tumor diameter could not be measured.

Eligibility criteria IRE

For IRE, 9 studies described cardiac arrhythmias or implanted electronical devices as exclusion criteria since IRE procedures need to be synchronized with ECG R-waves.[22,25,27-32] Maximum tumor size ranged from 35–60mm, mostly depending on the experience of the operator. A metal stent was described as a (relative) contra-indication in seven studies.[28-33,40] One animal study showed no vascular injury with electrodes placed within 1mm proximity of the PMV or mesenteric artery.[41] Other exclusion criteria were: a history of epilepsy[27-30], (uncorrectable) coagulopathy[22,28,42], coronary disease and a recent myocardial infarction.[28,30] In addition, for studies performing percutaneous IRE, there must be a window for a safe percutaneous approach without abdominal varices or the need for transcolonic electrode placement.[21,22] Multiple, overlapping ablations were not recommended since the post-IRE edema makes it difficult to place electrodes safely with ultrasound guidance.[35] Based upon literature, eligibility criteria were defined as shown in Table 2.

Table 2. Eligibility criteria for RFA and IRE

General criteria	
• Pathologically proven locally advanced, unresectable adenocarcinoma • Non-progressive disease after chemo(radio)therapy • No distant metastases • The ability to undergo general anaesthesia for IRE or deep sedation for RFA	
RFA criteria	**IRE criteria**
• A solid tumor bulk in order to place the smallest available RFA probe (9mm length) • The possibility to leave a 5mm safety margin between the estimated edge of the ablation zone (depending on the type of device/probe) and vital structures: - Portomesenteric vein - Superior mesenteric artery - Hepatic artery - Celiac trunc - Caval vein - Duodenum • Partial tumor ablation, ablation of peripancreatic fat and repeated ablations with replacements or pullback are allowed	• No history of a myocardial infarction within the last 6 month, epilepsy or cardiac arrhythmias • A maximum tumor diameter of 50mm • No >50% stenosis of both the portomesenteric vein ánd the common hepatic artery[a] • No partial thrombosis of the portal vein

RFA, radiofrequency ablation; IRE, irreversible electroporation

[a] based upon a case where a patient with a combination of a stenosis of the portal vein and common hepatic artery developed liver failure after IRE

Assessment of RFA and IRE eligibility

Upon reassessment, 53 patients (91%) were eligible for either RFA or IRE. In total, 36 patients (62%) were judged as eligible for RFA and 44 patients (76%) were eligible for IRE. There was an overlap of 27 patients (47%) between groups and 26 (45%) were eligible for only one treatment strategy (Figure 1). When excluding patients who underwent a resection (n=14) and patients who had metastases (n=4) at explorative laparotomy, the eligibility distribution did not change (n=35, 88% eligible for either RFA or IRE; n=25, 63% eligible for RFA; n=26, 65% for IRE; overlap in n=16, 40%). Table 3 summarizes the reasons for ineligibility for both treatment strategies. Imaging examples are shown in Figure 2.

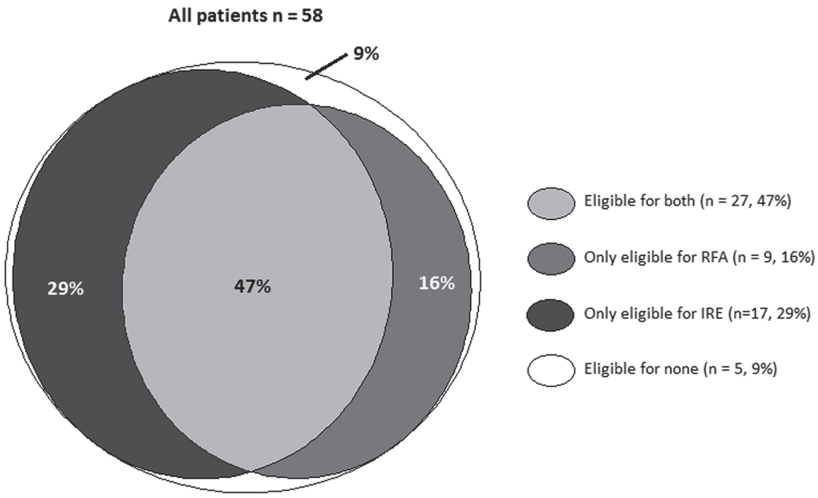

Figure 1. Venn diagram of treatment eligibility for IRE, RFA or both

Table 3. Reasons for ineligibility

	RFA (n = 22)	IRE (n = 14)
Deterioration of performance status after restaging, n (%)	2 (9)	2 (14)
Non-bulky, perivascular tumor growth, n (%)	13 (59)	-
Tumor between portomesenteric vein – duodenum without possibility to remain safety margin, n (%)	6 (27)	-
No tumor bulk visible on CT-scan, n (%)	1 (5)	-
Tumor diameter >5 cm, n (%)	-	8 (57)
Stenosis hepatic artery and portal vein, both >50%, n (%)	-	3 (21)
Portal vein thrombosis, n (%)	-	1 (7)

Table 4. Differences between groups eligible for RFA and IRE

Characteristics	RFA eligible, IRE ineligible (n = 9)	IRE eligible, RFA ineligible (n = 17)	Eligible for both (n = 27)	p-value
Tumor location, n (%)				
Head/uncinate process	3 (33)	11 (65)	22 (81)	**0.026**
Body/tail	6 (67)	6 (35)	5 (19)	
Tumor diameter, mm (SD)[a]	58 (8)	33 (15)	43 (12)	**<0.001**

SD, standard deviation; [a] missing case n = 2, one for both groups, tumor size could not be measured

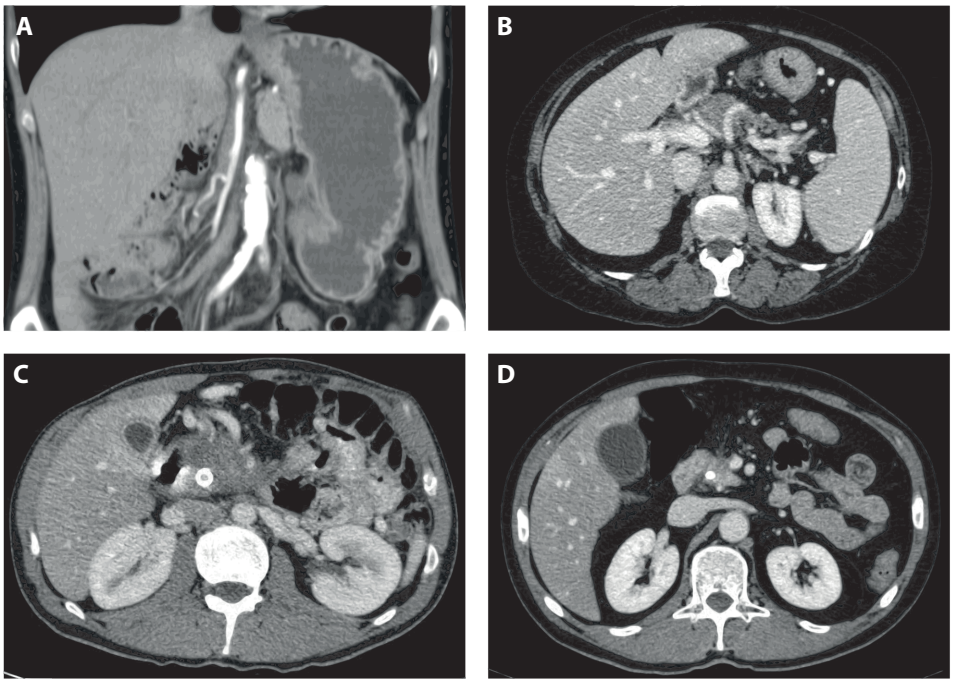

Figure 2. CT imaging of various scenarios of RFA and IRE eligibility
A. Ineligible for IRE due to tumor size >50mm, ineligible for RFA due
B. Eligible for IRE as well as RFA as the tumor has for RFA due to a non-bulky perivascular growth pattern of the tumor a bulky mass with adequate safety margins for RFA and is not above 50mm
C. Eligible for RFA, ineligible for IRE due to tumor size >50mmg
D. Eligible for IRE, ineligible for RFA due to a size >50mm small tumor between portomesenteric vein and duodenum without the possibility to remain safety margins

Tumors exclusively eligible for RFA were significantly larger than tumors eligible for IRE only or for both, with a largest diameter of 58mm (SD 8mm) versus 33mm (SD 15mm) versus 43mm (SD 12mm) respectively (p<0.001). Moreover, tumors exclusively eligible for RFA were more often located in the body/tail compared with tumors eligible for IRE only or for both (n=6, 67%; n=5, 19%; n=6, 35% respectively)(p=0.026)(Table 4).

DISCUSSION

This study identified eligibility criteria for IRE and RFA and classified the vast majority of patients with non-progressive LAPC after chemotherapy as eligible for either RFA or IRE. Overall, 62% of patients were eligible for RFA compared to 76% for IRE. IRE and RFA are equally complementary (45% of cases) as competitive (47% of cases). RFA appears to be most suitable for larger tumors (>50mm) located in the body/tail while IRE seems more suitable for small tumors with a perivascular growth pattern located in the pancreatic head.

Based on our overview of literature, it was evident that no standardized protocols or eligibility criteria for IRE and RFA exist. Even between studies from the same group different maximum tumor sizes were mentioned for IRE.[34,35,43] The current study defines tumors up to 50mm to be IRE eligible. Although challenging for less experienced practitioners, ablating tumors of 50mm is technically feasible.[29] For RFA, the distance from the electrode to vital structures was often described.[10,18,32,36-39] This is however an inaccurate technique of assessing eligibility, since different electrodes establish ablation zones with different size and shapes.[10] The current study defined a safety margin from the estimated edge of the ablation zone to vital structures, making it applicable to all different devices. A reduction of complications was seen when leaving an undefined safety margin between the ablation zone and vital structures. Together with animal studies, this was the basis of the established 5mm margin.[38,39,44] Compared with other studies evaluating only RFA or IRE, similar results of 57-83% eligibility for RFA and 57-84% eligibility for IRE were reported.[24,29,36,42]

Two non-randomized studies including a total of 350 patients with LAPC suggest that ablative control of the primary tumor can lead to a survival reaching 23.2 months after IRE[11] and 19 months after RFA.[8] According to the present study a considerable group of patients is eligible for only one of both ablative therapies. This points out the relevance of proceeding with RCTs on efficacy of RFA as well as IRE. Currently, the Dutch multicenter PELICAN trial is pending: a RCT comparing survival of RFA plus standard palliative chemotherapy with chemotherapy alone in patients with LAPC.[5] For patients eligible

for both modalities, future comparative studies should determine which treatment is superior. Until then, the responsible physician will play an important role in the decision between the two modalities, based on availability, his/her experience and ongoing studies. Furthermore, from this study it seems that larger lesions are more appropriate for RFA, while for smaller, perivascular growing tumors IRE is more appropriate.

The results of the present study must be interpreted in the light of some limitations. Although a literature search was performed to define eligibility criteria, there remains room for interpretation of the interventional radiologist. In addition, only one radiologist evaluated the eligibility for RFA and IRE. However this was a conscious choice based on his expertise in both treatment strategies for over many years minimizing confirmation bias when compared to an extra observer only practicing one of both therapies. Second, the current study does not investigate less invasive developments like endoscopic-ultrasound guided, percutaneous ablation, SBRT, microwave ablation or HIFU. This might become of more relevance within the near future.[45,4] Lastly, recent studies showed that post-FOLFIRINOX CT-scans cannot accurately identify vital tumor.[46] In the IMPALA study, 14 patients (24%) initially evaluated as LAPC with non-progressive disease after chemotherapy turned out to have resectable disease during explorative laparotomy. In addition, 4/36 patients who underwent an explorative laparotomy had peroperative occult metastasis.[13] This causes an overestimation of eligibility for ablative therapies in the current study. However, when excluding resected patients and patients with occult metastasis, eligibility distribution did not change.

CONCLUSIONS

The results of the current study show that no standardized criteria for RFA and IRE exist. The vast majority of patients with LAPC is eligible for at least one ablative treatment modality after chemotherapy. Since larger (>50mm) pancreatic body/tail lesions seem more appropriate for RFA and IRE seems more suitable for small non-bulky pancreatic head tumors, in 45% of cases RFA and IRE were complementary. This stresses the need to perform prospective RCTs on efficacy for both modalities, in order to determine the added value to current chemotherapy regimens and confirm which patients are suitable for RFA and IRE.

DECLARATIONS

Ethics

The IMPALA study was approved by the institutional ethical committee. Written informed consent was obtained for patients included in the IMPALA study.

Competing interests

KL is a paid consultant for AngioDynamics®. For all other authors, there are no conflicts of interest.

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Author's contributions

MW, JV, EV, MB and KvL contributed in the design of the study. MW and JV performed data collection for the study. KvL assessed all CT-scans and generated data for the manuscript. Analyses, figure and table design were performed by MW. Data interpretation was done by MW, JV and KvL. MW and JV were major contributors in writing the manuscript. All authors read, critically revised and approved the final manuscript.

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REFERENCES

1. Hidalgo M (2010) Pancreatic cancer. N Engl J Med 362:1605-1617
2. Vincent A, Herman J, Schulick R et al (2011) Pancreatic cancer. Lancet 378:607-620
3. Cid-Arregui A, Juarez V (2015) Perspectives in the treatment of pancreatic adenocarcinoma. World J Gastroenterol 21:9297-9316
4. Rombouts SJ, Vogel JA, van Santvoort HC, et al (2015) Systematic review of innovative ablative therapies for the treatment of locally advanced pancreatic cancer. Br J Surg 102:182-193
5. Dutch Trial Registry. PELICAN trial: local ablative treatment of an inoperable pancreascarcinoma. Trial ID: NTR 5517. Available at: www.trialregister.nl. Accessed 04/30, 2018
6. Dutch Trial Registry. CROSSFIRE trial: Comparing the Efficacy of Irreversible Electroporation with Radiotherapy. Trial ID: NTR5875. Available at: www.trialregister.nl. Accessed 04/30, 2018.
7. Giardino A, Innamorati G, Ugel S, et al (2017) Immunomodulation after radiofrequency ablation of locally advanced pancreatic cancer by monitoring the immune response in 10 patients. Pancreatology 17:962-966
8. Paiella S, Salvia R, Girelli R, et al (2016) Role of local ablative techniques (Radiofrequency ablation and Irreversible Electroporation) in the treatment of pancreatic cancer. Updates Surg 68:307-311
9. Davalos RV, Mir IL, Rubinsky B (2005) Tissue ablation with irreversible electroporation. Ann Biomed Eng 33:223-231
10. D'Onofrio M, Barbi E, Girelli R, et al (2010) Radiofrequency ablation of locally advanced pancreatic adenocarcinoma: an overview. World J Gastroenterol 16:3478-3483
11. Martin RC,2nd, Kwon D, Chalikonda S, et al (2015) Treatment of 200 locally advanced (stage III) pancreatic adenocarcinoma patients with irreversible electroporation: safety and efficacy. Ann Surg 262:486-94; discussion 492-4
12. Narayanan G, Hosein PJ, Beulaygue IC, et al (2017) Percutaneous Image-Guided Irreversible Electroporation for the Treatment of Unresectable, Locally Advanced Pancreatic Adenocarcinoma. J Vasc Interv Radiol 28:342-348
13. Vogel JA, Rombouts SJ, de Rooij T, et al (2017) Induction Chemotherapy Followed by Resection or Irreversible Electroporation in Locally Advanced Pancreatic Cancer (IMPALA): A Prospective Cohort Study. Ann Surg Oncol 24:2734-2743
14. Dutch Pancreatic Cancer Group (2017). Criteria for resectability according to the Dutch Pancreatic Cancer group (PREOPANC trial protocol). Available at: http:/www.dpcg.nl/projecten/preopanc. Accessed 10/16, 2017
15. Eisenhauer EA, Therasse P, Bogaerts J, et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228-247
16. Matsui Y, Nakagawa A, Kamiyama Y, et al (2000) Selective thermocoagulation of unresectable pancreatic cancers by using radiofrequency capacitive heating. Pancreas 20:14-20
17. Spiliotis JD, Datsis AC, Michalopoulos NV, et al (2007) Radiofrequency ablation combined with palliative surgery may prolong survival of patients with advanced cancer of the pancreas. Langenbecks Arch Surg 392:55-60
18. Wu Y, Tang Z, Fang H, et al (2006) High operative risk of cool-tip radiofrequency ablation for unresectable pancreatic head cancer. J Surg Oncol 94:392-395
19. Zou YP, Li WM, Zheng F, et al (2010) Intraoperative radiofrequency ablation combined with 125 iodine seed implantation for unresectable pancreatic cancer. World J Gastroenterol 16:5104-5110
20. Brown DB, Narayanan G (2012) Interventional radiology and the pancreatic cancer patient. Cancer J 18:591-601
21. Narayanan G, Hosein PJ, Arora G, et al (2012) Percutaneous irreversible electroporation for downstaging and control of unresectable pancreatic adenocarcinoma. J Vasc Interv Radiol 23:1613-1621
22. Venkat S, Hosein PJ, Narayanan G (2015) Percutaneous Approach to Irreversible Electroporation of the Pancreas: Miami Protocol. Tech Vasc Interv Radiol 18:153-158
23. Girelli R, Frigerio I, Giardino A, et al (2013) Results of 100 pancreatic radiofrequency ablations in the context of a multimodal strategy for stage III ductal adenocarcinoma. Langenbecks Arch Surg 398:63-69
24. Casadei R, Ricci C, Pezzilli R, et al (2010) A prospective study on radiofrequency ablation locally advanced pancreatic cancer. Hepatobiliary. Pancreat Dis Int 9:306-311

25. Kluger MD, Epelboym I, Schrope BA, et al (2016) Single-Institution Experience with Irreversible Electroporation for T4 Pancreatic Cancer: First 50 Patients. Ann Surg Oncol 23:1736-1743
26. Mansson C, Bergenfeldt M, Brahmstaedt R et al (2014) Safety and preliminary efficacy of ultrasound-guided percutaneous irreversible electroporation for treatment of localized pancreatic cancer. Anticancer Res 34:289-293
27. Mansson C, Brahmstaedt R, Nilsson A, et al (2016) Percutaneous irreversible electroporation for treatment of locally advanced pancreatic cancer following chemotherapy or radiochemotherapy. Eur J Surg Oncol 42:1401-1406
28. Paiella S, Butturini G, Frigerio I, et al (2015) Safety and feasibility of Irreversible Electroporation (IRE) in patients with locally advanced pancreatic cancer: results of a prospective study. Dig Surg 32:90-97
29. Scheffer HJ, Vroomen LG, de Jong MC, et al (2017) Ablation of Locally Advanced Pancreatic Cancer with Percutaneous Irreversible Electroporation: Results of the Phase I/II PANFIRE Study. Radiology 282:585-597
30. Tasu JP, Vesselle G, Herpe G, et al (2016) Irreversible electroporation for locally advanced pancreatic cancer. Diagn Interv Imaging 97:1297-1304
31. Weiss MJ, Wolfgang CL (2014) Irreversible electroporation: a novel therapy for stage III pancreatic cancer. Adv Surg 48:253-258
32. Paiella S, Salvia R, Ramera M, et al (2016) Local Ablative Strategies for Ductal Pancreatic Cancer (Radiofrequency Ablation, Irreversible Electroporation): A Review. Gastroenterol Res Pract 2016:4508376
33. Martin RC,2nd, Durham AN, Besselink MG, et al (2016) Irreversible electroporation in locally advanced pancreatic cancer: A call for standardization of energy delivery. J Surg Oncol 114:865-871
34. Martin RC, 2nd (2015) Use of irreversible electroporation in unresectable pancreatic cancer. Hepatobiliary Surg Nutr 4:211-215
35. Martin RC (2013) Irreversible electroporation of locally advanced pancreatic head adenocarcinoma. J Gastrointest Surg 17:1850-1856
36. D'Onofrio M, Crosara S, De Robertis R, et al (2017) Percutaneous Radiofrequency Ablation of Unresectable Locally Advanced Pancreatic Cancer: Preliminary Results. Technol Cancer Res Treat 16:285-294
37. Date RS, McMahon RF, Siriwardena AK (2005) Radiofrequency ablation of the pancreas. I: Definition of optimal thermal kinetic parameters and the effect of simulated portal venous circulation in an ex-vivo porcine model. JOP 6:581-587
38. Fegrachi S, Molenaar IQ, Klaessens JH, et al (2014) Radiofrequency ablation of the pancreas: two-week follow-up in a porcine model. Eur J Surg Oncol 40:1000-1007
39. Fegrachi S, Molenaar IQ, Klaessens JH, (2013) Radiofrequency ablation of the pancreas with and without intraluminal duodenal cooling in a porcine model. J Surg Res184:867-872
40. Dunki-Jacobs EM, Philips P, Martin RC,2nd (2014) Evaluation of thermal injury to liver, pancreas and kidney during irreversible electroporation in an in vivo experimental model. Br J Surg 101:1113-1121
41. Bower M, Sherwood L, Li Y, Martin R (2011) Irreversible electroporation of the pancreas: definitive local therapy without systemic effects. J Surg Oncol 104:22-28
42. Belfiore MP, Sciandra M, Romano F, et al (2015) Preliminary Results in Unresectable Head and Neck Cancer Treated by Radiofrequency and Microwave Ablation: Feasibility, Efficacy, and Safety. J Vasc Interv Radiol 26:1189-1196
43. Martin RC,2nd (2015) Irreversible electroporation of locally advanced pancreatic neck/body adenocarcinoma. J Gastrointest Oncol 6:329-335
44. Girelli R, Frigerio I, Salvia R, et al (2010) Feasibility and safety of radiofrequency ablation for locally advanced pancreatic cancer. Br J Surg 97:220-225
45. Pai M, Habib N, Senturk H, et al (2015) Endoscopic ultrasound guided radiofrequency ablation, for pancreatic cystic neoplasms and neuroendocrine tumors. World J Gastrointest Surg. 7:52-59
46. Ferrone CR, Marchegiani G, Hong TS, et al (2015) Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. Ann Surg 261:12-17
47. Dunki-Jacobs EM, Philips P, Martin RC,2nd. (2014) Evaluation of resistance as a measure of successful tumor ablation during irreversible electroporation of the pancreas. J Am Coll Surg Feb;218(2):179-187

SUPPLEMENTARY MATERIAL

Additional file 1. Search strategy

(Ablation[tiab] OR Ablation Techniques[Mesh] OR Ablation Technique*[tiab] OR Ablative[tiab] OR Irreversible electroporation[Tiab] OR IRE[Tiab] OR Nanoknife[Tiab] OR electroporat*[tiab] OR electroporese [tiab] OR radiofrequency ablation[tiab] OR RFA[tiab] OR radiofrequent ablation[tiab])

AND

((Pancreatic Neoplasms[Mesh] OR (Pancreas[tiab] AND cancer[tiab]) OR (Pancreatic[tiab] AND cancer[tiab]) OR (Pancreatic[tiab] AND adenocarcinoma[tiab]) OR (Pancreas[tiab] AND adenocarcinoma[tiab]) OR (Pancreatic[tiab] AND neoplasm*[tiab]) OR (pancreas[tiab] AND neoplasm*[tiab]) OR (malign*[tiab] AND pancreas[tiab]) OR (malign*[tiab] AND pancreatic[tiab]) OR (tumor[tiab] AND pancreas[tiab]) OR (tumors[tiab] AND pancreas[tiab]) OR (tumor[tiab] AND pancreatic[tiab]) OR (tumors[tiab] AND pancreatic[tiab]) OR (tumour[tiab] AND pancreas[tiab]) OR (tumour[tiab] AND pancreatic[tiab]) OR (tumours[tiab] AND pancreatic[tiab]))

AND

(Locally advanced[tiab] OR advanced[tiab] OR unresectable[tiab] OR irresectable[tiab] OR non-resectable[tiab] OR nonmetastatic[tiab] OR stage 3[tiab] OR stage III[tiab] OR T3[tiab] OR T4[tiab] OR nonresectability[tiab] OR non-metastatic[tiab] OR stage three[tiab]) OR LAPC[tiab])

Search date: 6th December 2017

Additional file 2. Summary of RFA studies

Reference	LAPC patients, n	RFA device, electrode	RFA temperature	Ablation diameter, mm	Safety distance from RFA probe, mm[a]	Other RFA specific eligibility criteria or safety measures
Casadei[24]	7	Cool-tip™ ablation system, Radionics™	90°C	NR	NR	NA
Date[37]	NA, animal study	RITA® system, Angiodynamics; StarBurst™ XL probe	80-100°C	20	20 (from duodenum, vessels NR)	NA
D'Onofrio[10]	NA, review article	Device NR; Two types of electrodes: 1.With expandable electrodes 2. With a single electrode	NR	10-60	5 (from the tip of the electrode)	1. The necrotic area must not overcome the lesion owing to the safety margins to main vascular and digestive structures 2. The occurrence of very small lesions/those that envelop the main vessels without a true mass is a contraindication for the procedure 3. Installation of cool water to the areas around the tumor during ablation: the duodenum is perfused with cold saline through nasogastric tubes and a cold wet gauze is placed over the inferior vena cava
D'Onofrio[36]	18	Mygen RF generator, RF Medical; VARI-Tip-VCT needle with internal cooling and 5-15mm active length	90°C	15-65	5 (from the tip of the electrode)	Percutaneous RFA: 1. A pancreatic body-tail tumor must be visible at percutaneous ultrasound 2. Dimensions greater than 2 cm 3. No abundant intralesional fluid component 4. US visualization of a safe needle tract 5. The necrotic area must not overcome the lesion
Fegrachi[38]	NA, animal study	CELON Power System Generator, Olympus; Water-cooled RFA probe with 30mm active length	90°C	20	15 (PMV)[b] 10 (duodenum(	1. Intraluminal duodenal cooling

Girelli23	100	RITA® System, Angiodynamics; StarBurst XL, Talon or UniBlate™ electrodes	90-105°C	NR	NR	1. A peripheral rim should be left and considered as a 'safety margin'to prevent thermal damage 2. A cold wet gauze was placed around the ablation area and the duodenum was cooled using a nasal duodenal tube 3. Temperature above 90°C doubles the risk of portal and/or mesenteric vein thrombosis, duodenal ulcer and bleeding
Matsui16	20	RF Generator, OMRON Co. Ltd.; four electrodes with 20mm active length, placed in a square array at intervals of 20mm	50°C	NR	NR	1. In the center of the four-needle electrode a thermosensor was inserted and temperature was monitored continually
Paiella32	NA, review article	NR	90°C	NR	15 (PMV) 10 (duodenum)	1. Tumor diameter is not a crucial as the technique allows ablation up to 5cm or more 2. Treat the biggest possible area, performing pull-backs of the tip, leaving a ' security rim' at the periphery of the tumor 3. Administer duodenal cooling with a cold saline solution through nasogastric tube
Spiliotis17	25	RF generator, Radionics; Cool-tip™ RF probes with 30mm active length	90°C	NR	NR	1. Continuous infusion/perfusion of the area with cold normal saline was done to maintain surrounding tissue <35°C 2. Target temperature was controlled by a thermosensor at the tip of the needle
Wu18	16	RFA generator, Radionics; cooled-tip RFA probe with 20-30mm active length	30-90°C	NR	5	1. A thermocouple was on the tip of the probe to monitor temperature 2. Tumors larger than 3 cm received overlapping ablations 3. A 5 mm minimum safe distance to portal vein might not be enough
Zou[19]	32	RITA® System, Angiodynamics; Uniblate™ electrode with 10-30mm active length	90-100°C	10-25	NR	1. Temperature sensor at tip of needle 2. Cool down cycle (not further specified) 3. Ablation should be restricted within the tumor

RFA, radiofrequency ablation; PMV, portomesenteric vein; NA, not applicable; NR, not reported; [a]Distance of RFA probe from vital structures such as the duodenum and peripancreatic vessels; ; [b] Based on experiments with probe placement at 5 or 15mm from the PMV/duodenum and temperature measurement at 5, 10 and 15mm from the RFA probe

Additional file 3. Summary of IRE studies

Reference	LAPC patients, n	IRE device, electrode	Open vs. percutaneous	Maximum tumor size, mm	Other IRE specific eligibility criteria
Belfiore [42]	20	Nanoknife system, Angiodynamics; 15mm active length, electrode spacing 20mm	Percutaneous	60 (axial)	1. No moderate-severe cardiopulmonary failure or coagulation disorders
Bower[41]	NA, animal study	Nanoknife system, Angiodynamics; electrode spacing 15-20mm	Open	NA, healthy pancreatic tissue	1. Electrodes placed 1mm from portal vein or SMA showed no thermal injury, so no minimum distance to vital structures is advised
Brown[20]	14	Device NR, electrode spacing 22mm	Percutaneous	NR	1. Multidisciplinary team of medical oncologists, interventional radiologists, surgeons and radiation oncologists determined eligibility for IRE
Dunki-Jacobs[40]	NA, animal study	Nanoknife system, Angiodynamics; 19-gauge monopolar; electrode spacing 20mm	Open	NA, healthy pancreatic tissue	1. It is recommended that metal structures (such as biliary stents) be removed before IRE. If this is not feasible, the probe pairs should not bracket the metal and if possible be at least 1cm away from the IRE probes.
Dunki-Jacobs[47]	65	Nanoknife system, Angiodynamics; 10-15mm active length, electrode spacing 18mm	Both	NR	1. References to Martin *e al*[35]
Kluger[25]	29	Nanoknife system, Angiodynamics; 10-15mm active length, electrode spacing 20mm	Open	30	1. Atrial fibrillation was a contraindication for IRE
Mansson[26]	5	Nanoknife system, Angiodynamics; 15mm active length, electrode spacing 20mm	Percutaneous	NR	1. The aim was to cover the entire tumor area with a 5mm safety margin, therefore replacement and retraction was performed 2. All patients had defibrillation pads put in place
Mansson[27]	24	Nanoknife system, Angiodynamics; 15mm active length, electrode spacing 25mm	Percutaneous	50	1. Implanted electronic devices, severe heart disease and epilepsy were exclusion criteria 2. No needle placement through stomach or bowel

Reference	LAPC patients, n	IRE device, electrode	Open vs. percutaneous	Maximum tumor size, mm	Other IRE specific eligibility criteria
Martin[35]	NA, 'how I do it'	Device NR, 10-15mm active length; electrode spacing 20mm	Open	35 (axial)	1. Pullbacks are allowed, but without overlapping treatment area 2. Removal of metal stents is critical
Martin[34]	NA, review article	Device NR; 10-15mm active length; electrode spacing 17-22mm	Open	30 for new users, 40 for more experienced users	NR
Martin[33]	NA, 'how I do it'	Nanoknife system, Angiodynamics; 10-15mm active length; electrode spacing 20-27mm	Open	40 (axial)	1. Metal stents should be removed before IRE since it can lead to deflection of energy, incomplete ablation and possible thermal injury 2. Use a caudal-to-cranial approach of needle placement
Martin[11]	200	Nanoknife system, Angiodynamics; maximum 10mm active length	Open	NR	1. A series of pull-backs was required with sequential electroporation 2. Reference to Martin et al[35]
Narayanan[21]	14	Nanoknife system, Angiodynamics; electrode spacing maximum 22mm	Percutaneous	NR	1. A history of cardiac arrhythmias was an exclusion criterium 2. If there was no clear window to access the tumor could be established due to esophageal, gastric or splenic varices, the patient was excluded for IRE 3. Pull-back was performed if target treatment zone was greater than 2cm to cover the entire target
Paiella[28]	10	Nanoknife Low Energy Direct Current System, Angiodynamics; electrode spacing 10-20mm apart	Open	40	Exclusion criteria 1. Not able to stop antiplatelet and coumarine derivates for 7 days prior and 7 days post treatment 2. A history of epilepsy, cardiac arrhythmias or a myocardial infarction within the past 2 months 3. Implanted cardiac pacemakers or defibrillators, electronic devices or implants with metal parts in the vicinity of the lesion 4. Not able to remove metallic biliary/duodenal stent

Additional file 3. Summary of IRE studies

Reference	LAPC patients, n	IRE device, electrode	Open vs. percutaneous	Maximum tumor size, mm	Other IRE specific eligibility criteria
Paiella[32]	NA, review article	NR	NA, review article	NR	1. IRE works better on tumor sizes 3-3.5cm 2. IRE is contraindicated in patients with pacemakers or cardiac arrhythmias 3. A metallic biliary stent should be removed intraoperatively
Scheffer[29]	25	Nanoknife system, Angiodynamics; 15mm active length, electrode spacing 25-24mm apart	Percutaneous	50 (axial)	Exclusion criteria: 1. A metallic biliary Wall stent 2. A history of ventricular cardiac arrhythmias, epilepsy 3. Any implanted stimulation device
Tasu[30]	NA, review article	Device NR; electrode spacing 10-25mm	Percutaneous and open	NR	1. The needle need to be positioned at least 2mm away from large vessels 2. A metal stent is a contraindication for IRE 3. Cardiac arrhythmias, heart failure, epilepsy and active coronary disease are contraindications for IRE
Venkat[22]	NA, review article	Nanoknife system, Angiodynamics; 10-15mm active length, electrode spacing 10-22mm	Percutaneous	IRE can be performed in a staged approach for lesions >5cm in case of no down-staging after chemotherapy	Exclusion criteria: 1. Patients with cardiac arrhythmias 2. Unsafe access for a percutaneous approach such as overlying colon obscuring the window or varices in the approach of the lesion 3. Patients with uncorrectable coagulopathy
Weiss[31]	NA, review	NR	Open	35	1. Pre-existing cardiac conduction abnormalities is an exclusion criteria 2. Metallic biliary stents usually need to be removed if they are within the anticipated electroporation field, but are not considered an absolute contraindication

IRE, irreversible electroporation; NA, not applicable; NR, not reported

Chapter 9

Safety of radiofrequency ablation in patients with locally advanced, unresectable pancreatic cancer: a phase II study

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ABSTRACT

Background

Radiofrequency ablation (RFA) has been proposed as a new treatment option for locally advanced, unresectable pancreatic cancer (LAPC). In preparation of a randomized controlled trial (RCT), the aim of this phase II study was to assess the safety of RFA for patients with LAPC.

Methods

Patients diagnosed with LAPC confirmed during surgical exploration between November 2012 and April 2014 were eligible for inclusion. RFA probes were placed under ultrasound guidance with a safety margin of at least 10mm from the duodenum and 15mm from the portomesenteric vessels. During RFA, the duodenum was continuously perfused with cold saline to reduce risk for thermal damage. Primary outcome was defined as the amount of major complications (Clavien-Dindo grade III). RFA-related complications were predefined as: pancreatic fistula, pancreatitis, thermal damage to the portomesenteric vessels and duodenal perforation.

Results

In total, 17 patients underwent RFA. Delayed gastric emptying (DGE) requiring endoscopic feeding tube placement occurred in 4 patients (24%) as only major complication. Five patients (29%) had a major complication other than DGE. One (6%) RFA-related major complications occurred. One patient (6%) died due to complications from a biliary leak following hepaticojejunostomy. After evaluation of the first 5 patients, gastrojejunostomy was no longer performed routinely. Since then severe DGE seemed to occur less (3/5 vs. 3/12 grade C DGE).

Conclusion

RFA is a major, but safe procedure for patients with LAPC if performed with strict predefined safety criteria. A RCT is currently investigating the true effectiveness of RFA in patients with LAPC.

INTRODUCTION

Pancreatic cancer is among the most aggressive cancers and estimated to become the number two leading cause of cancer related death in the near future.[1] Overall survival hardly improved over the last decades.[2] Surgical resection combined with (neo-)adjuvant chemotherapy provides the best chances of long-term survival but is only feasible in a minority of patients. About 30-40% of patients present without distant metastases, but with unresectable disease at the time of diagnosis due to involvement of important vascular structures.[3] Currently, standard treatment for these patients with locally advanced, unresectable pancreatic cancer (LAPC) is palliative systemic chemotherapy.

Interestingly, several new treatment strategies for LAPC have become available. Radiofrequency ablation (RFA) is one of those techniques aiming for local tumor destruction through application of a high frequency alternating current. With this thermal-based technique one or more electrodes are implanted centrally into the tumor to induce cell death by frictional heating.[4] It has recently been shown that RFA may also induce a systemic immune response in pancreatic cancer, different from normal surgical stress, possibly due to a transitional zone of apoptosis-undergoing tumor tissue exposing tumor-specific antigens.[5] It is hypothesized that this can result in a systemic anti-tumor immune response that can improve overall survival. Non-randomized studies showed promising overall survival up to 25.6 months after RFA for LAPC.[6] However, no randomized controlled trials (RCTs) have been performed, so the true effectiveness of RFA combined with systemic chemotherapy regimens remains unknown. Moreover, morbidity rates range from 14% to 28% and seems to depend on RFA temperature settings, preventive duodenal cooling, and safety margins from vital structures.[6-8] In preparation for an international multicenter RCT, this prospective single-center observational phase II study aims to assess the safety of RFA for patients with LAPC.

METHODS

Study population and study design

Patients diagnosed with histologically proven borderline resectable pancreatic cancer and LAPC underwent an explorative laparotomy with the intention for resection. If the tumor turned out to be unresectable during surgical exploration without metastases, patients were eligible for inclusion. Exclusion criteria were: portal vein thrombosis, inability to achieve predefined safety margins to vital structures, age below 18 years and pregnancy. Preoperative staging was based on a multiphasic contrast-enhanced computed tomography (CT) scan, discussed at the multidisciplinary meeting and

defined according to the consensus criteria of the Dutch Pancreatic Cancer Group.[9] Intra-operative resectability was determined by surgical expertise and based on the vascular tumor encasement: >180° of arterial contact or venous unreconstructable disease were defined unresectable. Both patients with and without preoperative chemotherapy treatment were eligible for inclusion.

The study meets all guidelines of the Dutch responsible governmental agency, was approved by the institutional ethical committee and registered at clinicaltrials.gov (identification number: NCT01628458). All patients provided written informed consent before surgical exploration. An independent data and safety monitoring board (DSMB) conducted a review and evaluation of the safety of the data after every 5 patients.

Radiofrequency ablation procedure

All patients received prophylaxis for surgical site infections (cefazolin 2 g/metronidazole 500 mg), pancreatic fistulas (octreotride) and deep vein thrombosis (low molecular weight heparin). Patients underwent explorative laparotomy under general anesthesia. The peritoneal cavity was explored for possible metastases, and Kocher maneuver performed to expose the pancreatic head. In case of unresectable pancreatic cancer, the surgical team proceeded with RFA. RFA was carried out by an interventional radiologist with the multipolar CelonLab® POWER System generator and Celon-ProSurge® probes with exposure lengths of 20/30/40mm(Olympus Surgical Technologies Europe, Teltow, Germany). A total of 15 kJ per probe was delivered with a power setting of 1W per mm probe length as previously investigated.[7,8] Before ablation a cold wet gauze was placed over the inferior caval vein and the duodenum was continuously perfused with cold saline through 2 nasogastric tubes to reduce the risk for thermal damage. The RFA probe was placed in the center of the tumor under direct ultrasound guidance. A distance of the probe of at least 10mm from the duodenum and 15mm from the portomesenteric vessels (i.e. portal vein, superior mesenteric vein, superior mesenteric artery, celiac trunc, common hepatic artery) and surrounding vital structures was remained and the ablation zone was planned to not exceed the tumor in accordance with previously published studies.[7,8,10] In case of pancreatic head cancer in the first 5 patients a biliary and gastric bypass were performed routinely for palliative reasons and to prevent the consequences of possible RFA induced biliary damage. After evaluation of the first 5 procedures with the DSMB, gastrojejunostomy was only performed in case of high risk of gastric obstruction, since a relatively high amount of delayed gastric emptying (DGE) was observed. An abdominal drain was left in the omental bursa.

Outcome measures

The primary endpoint of the study was safety defined as the number of patients with major complications (i.e. Clavien-Dindo grade ≥III) within 30 days or during the initial

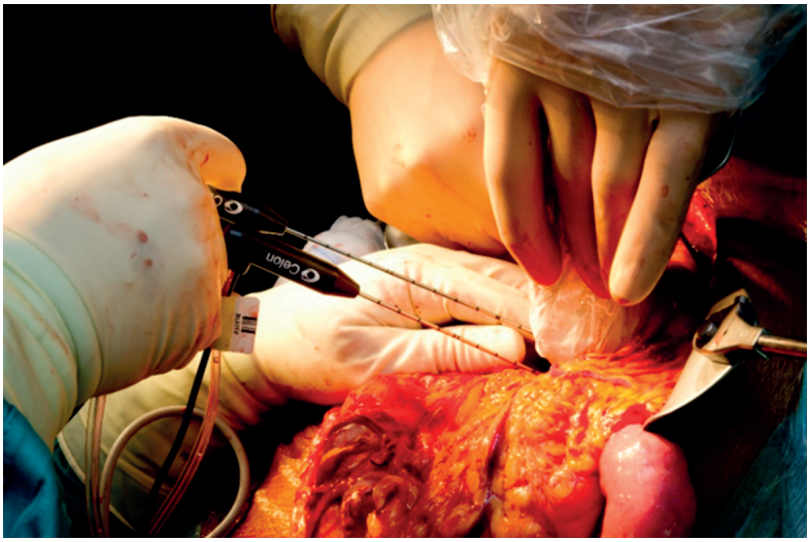

Figure 1. Intra-operative placement of RFA probe under direct ultrasound guidance

admission. All complications were scored according to Clavien-Dindo classification.[11] Postoperative pancreatic fistula, DGE, post-operative hemorrhage, bile and chyle leakage were classified according to the definitions of the International Study Group on Pancreatic Surgery (ISGPS) as well, but only grade B/C complications were included.[12-15] For comparability with previous studies, RFA-related complications were predefined as: pancreatic fistula, pancreatitis, thermal damage to the portomesenteric vessels and duodenal perforation.[9] Secondary outcome parameters were late complications, length of hospital stay, CA19-9 response and overall survival. At day 7 after the RFA procedure, a 2-phase pancreatic CT-scan was performed. The study had a follow-up period of 3 months for late complications, afterwards only survival data was collected.

Sample size and statistics

Based upon a systematic review involving 158 patients with pancreatic cancer treated with RFA from 5 studies, the proportion of RFA-related complication Clavien-Dindo grade ≥III was expected to be approximately 12%.[16] Together with an expected complication rate after combined biliary and gastric bypass of 14%[17] a maximum acceptable rate of 25% was defined. As this study was a safety study, a power of 0.50 was chosen to detect any unsafe situation of the treatment as early as possible. Using an expected occurrence of 12% with a fixed undesirable upper reference bound of 25%, in order to have a power of 0.50 with a one-sided a of 0.05, a total of 17 patients were needed and at most 5 were allowed to have a major complication (binomial test for one proportion).[18]

Statistical analysis was performed with SPSS statistical software (SPSS Statistics Version 22.0, Inc., Chicago, Illinois, USA). Patient characteristics and study outcomes were presented with descriptive statistics using mean with standard deviation or median with interquartile range when appropriate for continuous data and number with percentage for categorical data.

RESULTS

Between November 2012 and April 2014, 34 patients underwent an explorative laparotomy and 13/34 patients were treated with a surgical resection. Another 4 patients were excluded from RFA due to absence of a safety margin to vital structures on intra-operative ultrasound (n=2), concomitant pancreatitis (n=1), or peritoneal metastases (n=1). The remaining 17 patients turned out to have
LAPC and were included for RFA. Demographics of these patients and tumor characteristics are shown in Table 1. Procedural details are given in Table 2 and Figure 1 shows an image of intra-operative RFA probe placement under direct ultrasound guidance. A preoperative CT-scan, intra-operative ultrasound during the RFA procedure, and a post-procedural CT-scan within the same patient are shown in Figure 2 in order to visualize the procedure in more detail.

Overall complications

All major complications that occurred within 30 days are depicted in Table 3. A Clavien-Dindo grade ≥III complication occurred in 9 patients (53%). A common problem was DGE requiring endoscopic tube placement in 8 patients (47%). In 4 of them (24% of all patients) this was the only major complication. After a gastrojejunostomy bypass was no longer performed routinely, DGE complications seemed less frequent and less severe (Table 4). In total, 5 patients (29%) had a Clavien-Dindo grade III complication other than DGE. One patient (6%) died 57 days after the RFA procedure due to an ongoing deterioration after a hepaticojejunostomy leakage with multiple intra-abdominal abscesses, cholangiosepsis with liver abscesses and respiratory failure. One patient (6%) had a bleed from a pseudoaneurysm of the gastroduodenal artery after RFA of a tumor in the uncinate process. The aneurysm was successfully coiled during angiography. Three weeks after coiling, this patient had melena due to a bleeding ulcer at the gastrojejunostomy that could be treated endoscopically. One patient (6%) required a percutaneous hepatic biliary drainage under general anesthesia, because of a biliary leak from the hepaticojejunostomy. This patient developed a pneumosepsis requiring admission to the medium care without the need for invasive ventilation. Other major complications were: ultrasound guided drainage of ascites in a patient with a pre-existing portomesenteric vein (PMV) occlusion

Table 1. Patients and tumor characteristics

Characteristic	All patients n = 17
Age, years (SD)	62 (11)
Male sex, n (%)	7 (41)
Tumor location, n (%)	
Head/uncinate process	13 (76)
Body/tail	4 (24)
Biggest tumor diameter, mm (SD)	48 (11)
Vascular involvement, n (%)	
Superior mesenteric artery	12 (71)
0° – 90°	2 (12)
90°- 180°	2 (12)
>180°	8 (47)
Celiac trunk	7 (41)
0° – 90°	1 (6)
90°- 180°	-
>180°	6 (35)
Portal vein	12 (71)
0° - 270°	4 (24)
>270°	8 (47)
Superior mesenteric vein	16 (94)
0° - 270°	7 (41)
>270°	9 (53)
Significant stenosis/occlusion of portomesenteric vein, n (%)	14 (82)
Pre-treated with chemotherapy, n (%)	3 (18)
FOLFIRINOX	2 (12)
Gemcitabine based	1 (6)

(n=1, 6%) and pneumosepsis with medium care admission without the need for invasive ventilation (n=1, 6%). According to ISGPS definitions 4 patients (24%) had a grade B chyle leakage, but this did not require a re-intervention.

RFA-related complications

No major pancreatic fistulas, pancreatitis or duodenal perforations occurred. The described pseudoaneurysm in 1 patient (6%) was probably related to thermal damage to the gastroduodenal artery. Other thermal effects to the PMV only resulted in minor complications (Clavien-Dindo grade II): 4 patients (24%) were diagnosed with a new thrombus of the PMV one week after RFA (Figure 2c). All 4 had a significant stenosis of the PMV caused by tumor encasement in advance of the RFA procedure. These patients had no clinical symptoms and were treated with low molecular weight heparine. One of them was readmitted 44 days after the procedure with abdominal pain and ascites, which was drained under ultrasound guidance. One patient had a thrombus in the left renal vein, without any clinical symptoms.

Secondary outcomes

During 3 months follow-up, 2 patients had additional major complications. One patient had a retrogastric fluid collection that was transgastrically drained 58 days after the RFA procedure. The second patient developed hematemesis 73 days after the procedure based on an arterial bleed at the gastrojejunostomy that could be clipped endoscopically. Two other patients showed a peripancreatic fluid collection on CT-scan during follow-up, but without any clinical signs, so no drainage or intervention was performed. The median postoperative hospital stay was 15 days (IQR 8e23). The postoperative CA19-9 value decreased from a median preoperative value of 315 (IQR 123e1205) to a median of 180 (IQR 70-500) and 180 (IQR 63-588) on day 7 and 3 months after the operation respectively. Median overall survival was 9 months (IQR 5-11 months).

Table 2. Procedural details

Characteristic	All patients n = 17
Bypass surgery, n (%)	
Hepatico- and gastrojejunostomy	8 (47)
Hepaticojejunostomy only	5 (29)
No bypass[a]	4 (24)
Additional procedures, n (%)	
Small bowel resection[b]	1 (6)
No. of RFA probes used per procedure, n (%)	
1	4 (24)
2	11 (65)
3	1 (6)
4	1 (6)
Ablation time, min:sec, median (IQR)	20:42 (14:34 – 29:02)

[a] One patient underwent a previous exploration elsewhere with a hepatico- and gastrojejunostomy.
[b] Because of adhesion of the small bowel with the tumor, one patient received a small bowel resection with a duodenojejunostomy.

Table 3. Major complications during hospital stay or within 30-days after RFA pancreas defined by Clavien-Dindo classification ≥III and ISGPS

	All patients n = 17
Overall complications, n (%)[a]	9 (53)
Overall RFA-related complications, n (%)	1 (6)
Clavien Dindo classification	
Clavien-Dindo grade IIIa, n (%)[A]	9 (53)
DGE with endoscopic tube placement	8
Ascites drained under ultrasound guidance	1
Melaena (bleeding ulcer at GJ)	1
Clavien-Dindo grade IIIb, n (%)	1 (6)
Biliary leak from HJ	1
Clavien-Dindo grade IVa, n (%)	3 (18)
Pneumosepsis (medium care admission)	2
Hemorrhage with coiling pseudoaneurysm from gastroduodenal artery	1
Clavien-Dindo grade IVb, n (%)	-
Clavien-Dindo grade V, n (%)	1 (6)
Biliary leak from HJ with cholangiosepsis, intra-abdominal abscesses and respiratory failure	1
ISGPS classification	
Pancreatic fistula	-
Bile leakage, n (%)	2 (12)
Grade B	1
Grade C	1
Postoperative hemorrhage, n (%)	1 (6)
Grade B	1
Delayed gastric emptying, n (%)	8 (47)
Grade B	2
Grade C	6
Chyle leakage, n (%)	4 (24)
Grade B	4

[a] Since some patients had more than one major complication, all separate complications do not sum up to total number of complications. DGE: delayed gastric emptying, GJ: gastrojejunostomy, HJ: hepaticojejunostomy, ISGPS: International Study Group on Pancreatic Surgery.

Table 4. Relationship between gastrojejunostomy and DGE

	Gastrojejunostomy	**DGE Grade B/C**	**DGE Grade C**
Period 1 (n = 5)	3 (60%)	3 (60%)	3 (60%)
Period 2 (n = 12)	5 (42%)	5 (42%)	3 (25%)

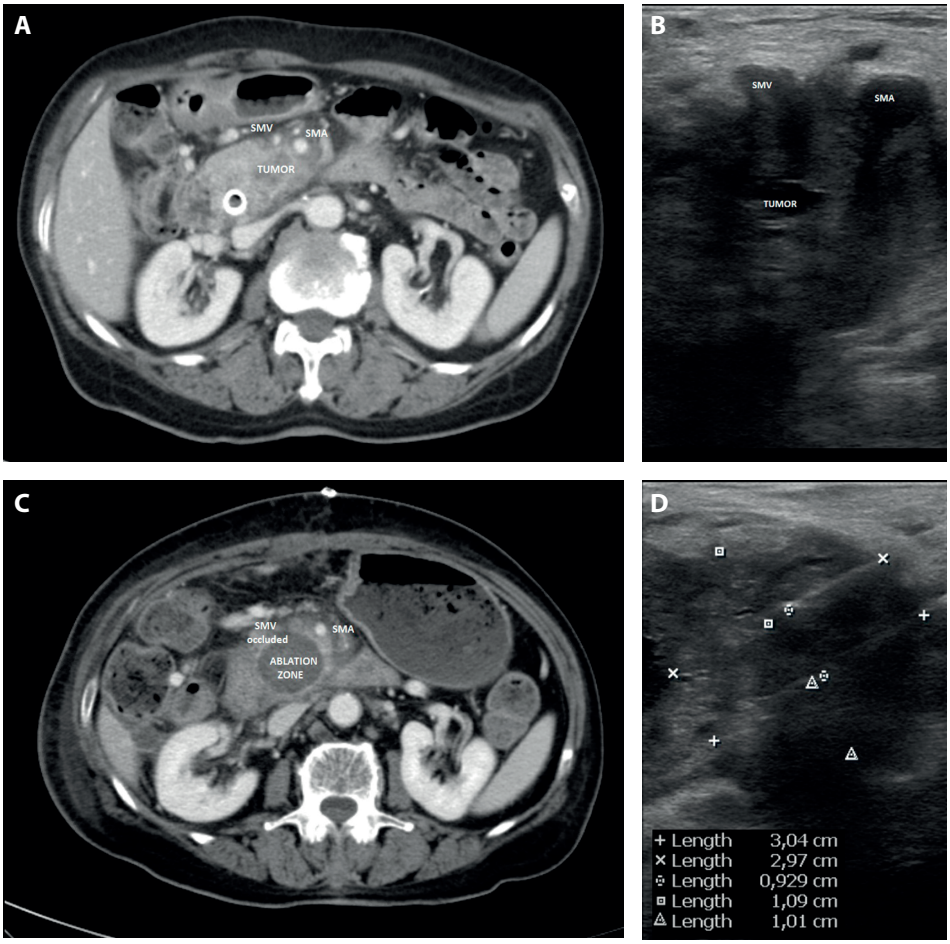

Figure 2. Preoperative CT-scan, intra-operative ultrasound and post-operative CT-scan in a patient with LAPC treated with RFA

2a: preoperative CT-scan with >270 contact with superior mesenteric artery (SMA) and superior mesenteric vein (SMV);

2b: intra-operative ultrasound showing the same configuration as the CT-scan;

2c: postoperative CT-scan one week after RFA pancreas shows a distinct ablation area and an occluded superior mesenteric vein without further complications;

2d: example of intra-operative ultrasound measurements with two 3 cm RFA probes (between plus signs and multiplication signs respectively) placed 1 cm width apart.

DISCUSSION

The present observational phase II study showed that after RFA of the pancreas major morbidity could mainly be attributed to DGE with the need for endoscopic tube placement (8 patients; 46%). DGE seemed to occur mostly as a result of the surgical gastrojejunostomy that were performed routinely in case of pancreatic head cancer in the first 5 patients of the study. After a gastrojejunostomy was performed only when indicated, DGE occurred less often and was less severe. In 5 patients (29%) a major complication other than DGE occurred, 1 patient (6%) developed a major RFA-related complication and 1 patient (6%) died 57 days after the procedure due to leakage of the hepaticojejunostomy.

One of the first studies reporting on RFA of the pancreas in 16 patients with LAPC described a relatively high amount of complications, with a mortality rate of 25%. This study ablated with a probe tip temperature exceeding 90 °C at a 5-mm safety distance from the probe to vital structure and each patient underwent 2-5 sessions of ablations.[19] The Verona group optimized the safety of the procedure by lowering ablation temperature to a maximum of 90 °C and performing a more prudent ablation, aiming to leave an undefined peripheral rim of tumor as a safety margin to surrounding tissues.[10] With these measures, they were able to lower morbidity rates from 40% to an overall complication rate of 26% in 100 patients treated with RFA. A RFA-related complication occurred in 15% of patients. In the present study the minimum distance of the RFA probe to vital structures was further defined as at least 10mm from the duodenum and 15mm from the portomesenteric vessels. With this more specific safety criteria, RFA-related complications as defined in previous studies occurred in only 1 patient (6%). Although hepaticojejunostomy leakage occurred in a notable high proportion of patients (n ¼ 2, 12%), it is unlikely to be a direct thermal effect of the RFA procedure since the hepaticojejunostomy was performed after the RFA procedure and at a reasonable distance from the ablated area. Future studies with larger sample sizes should pay attention to this specific complication and might investigate the possibility of omitting a hepaticojejunostomy in the presence of a metal stent.

Compared to the study of Girelli *et al*.,[10] the overall major complication rate was higher (53% compared to 26%). This might be explained by the use and interpretation of the Clavien-Dindo classification. In the present study, endoscopic feeding tube placement caused all DGEs to be classified as a grade 3a complication, while other centers might place tubes intra-operatively, without endoscopy, or simply not interpret tube placement as a major complication. For example, although a gastrojejunostomy was performed in 43/100 patients, no cases of DGE were described in the study of Girelli *et al*.[10,20] This,

while other studies describe up to 30% DGE after palliative doubly bypass surgery for pancreatic adenocarcinoma.[21,22] When DGE is not considered as major complication, the complication rate is within the predefined acceptable amount (5 patients, 29%) and comparable to the Verona group (29% versus 26%). Together with less RFA-related complications this supports that despite the high rate of DGE and the possibility of thermal damage, the current study establishes the safety of RFA pancreas in patients with LAPC.

Regarding overall survival, the present study is not comparable to other studies because RFA was given as upfront therapy in the majority of patients. This was deliberately chosen, since the aim of the study was to investigate the safety rather than efficacy. Moreover, the standard treatment at the time of this study was primary surgery and in case of inoperability gemcitabine monotherapy. This chemotherapeutic regimen only demonstrated an improvement of symptoms and benefit concerning survival is very limited.[23] In the current era, where new chemotherapeutic regimens like FOLFIRINOX have proven their superiority and where neoadjuvant treatment has become standard treatment, local ablative therapies should be used in the context of a multimodal treatment strategy.[24,25]

This study provides unique data as the effects of only RFA treatment could be evaluated, without interference of other treatments. Strengths of this study include the strict and predefined safety measures. First, a systematic literature review was performed.[16] Second, the Verona hospital was visited in order to be trained by longstanding and highly regarded international experts in the field. To further specify optimal RFA settings, animal studies were performed upon which safety distances from the probes in the current study were based.[7,8] The optimization of these criteria introduces a safe RFA pancreas procedure. Because of the pilot nature of the study and the monitoring of complications after every 5 patients, it was possible to optimize the procedure along the way and the possible influence of gastrojejunostomy could be clarified during the study. Some aspects of the study should be interpreted with care. Since this study was not designed to investigate efficacy of RFA, overall survival might not be representative. Moreover, the current study investigated RFA in the open setting while more recent studies also reported the feasibility of minimal invasive ablation.[26,27] This can reduce laparotomy related morbidity, but probe placement is performed in a less controlled setting. Therefore safety of endoscopic-ultrasound guided or percutaneous RFA should be a subject of further investigation synchronously along with the current efficacy studies in the open setting.

Non-randomized studies report a survival of 25.6 months in patients pre-treated with systemic therapy followed by ablative control of the primary tumor.[25] However, more recently FOLFIRINOX has become the preferred chemotherapeutic regimen and promising overall survival of up to 25 months have been described for patients treated with FOLFIRINOX without ablative therapy.[28,29]

Therefore, the true effectiveness of RFA in addition to the current chemotherapy regimens remains unclear. Based on the current observational phase II study an international multicenter RCT was designed: the PELICAN trial.[30] This study compares overall survival in patients with non-progressive LAPC after 2 months of induction chemotherapy who are either treated with RFA plus chemotherapy versus chemotherapy alone. PELICAN is currently the only ongoing RCT investigating ablative therapy in combination with induction chemotherapy for this patient population, and the results will be of great relevance. At this moment, inclusion in the PELICAN trial is halfway (114/228).

CONCLUSION

In conclusion, RFA pancreas should be considered as a major procedure with the risk of thermal damage to nearby vital structures. However, when strict safety measures are taken it can be considered safe with approximately 25% major morbidity. A gastrojejunostomy should not be performed routinely since this might contribute to severe gastric delayed emptying. Considering the current dismal prognosis of patients with LAPC the possible survival benefit of RFA combined with current improving chemotherapeutic regimens should be investigated within a RCT. This trial is currently ongoing.[30]

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DECLARATION OF INTEREST

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REFERENCES

1. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014;74:2913e21.
2. American Cancer Society. Cancer facts and figures 2018, vol. 18; 2018. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-andstatistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf. [Accessed 18 July 2018].
3. Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer Lancet 2011;378:607e20.
4. Paiella S, Salvia R, Girelli R, Frigerio I, Giardino A, D'Onofrio M, et al. Role of local ablative techniques (Radiofrequency ablation and Irreversible Electroporation) in the treatment of pancreatic cancer. Updates Surg 2016;68:307e11.
5. Giardino A, Innamorati G, Ugel S, Perbellini O, Girelli R, Frigerio I, et al. Immunomodulation after radiofrequency ablation of locally advanced pancreatic cancer by monitoring the immune response in 10 patients. Pancreatology 2017;17:962e6.
6. Rombouts SJE, Vogel JA, Van Santvoort HC, Van Lienden KP, Van Hillegersberg R, Busch ORC, et al. Systematic review of innovative ablative therapies for the treatment of locally advanced pancreatic cancer. Br J Surg 2015;102:182e93.
7. Fegrachi S, Molenaar IQ, Klaessens JH, Besselink MG, Offerhaus JA, Van Hillegersberg R. Radiofrequency ablation of the pancreas: two-week followup in a porcine model. Eur J Surg Oncol 2014;40:1000e7.
8. Fegrachi S, Molenaar IQ, Klaessens JH, Besselink MG, Offerhaus JA, Van Hillegersberg R. Radiofrequency ablation of the pancreas with and without intraluminal duodenal cooling in a porcine model. J Surg Res 2013;184:867e72.
9. Dutch Pancreatic Cancer Group. Definitions of resectability pancreatic cancer. http://www.dpcg.nl/richtlijnen-classificaties/dpcg-definities.html. [Accessed 13 March 2019].
10. Girelli R, Frigerio I, Giardino A, Regi P, Gobbo S, Malleo G, et al. Results of 100 pancreatic radiofrequency ablations in the context of a multimodal strategy for stage III ductal adenocarcinoma. Langenbeck's Arch Surg 2013;398:63e9.
11. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205e13.
12. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years after. Surgeon 2017;161:584e91.
13. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 2007;142:761e8.
14. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, et al. Postpancreatectomy hemorrhage (PPH)-An international study group of pancreatic surgery (ISGPS) definition. Surgery 2007;142:20e5.
15. Koch M, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L, et al. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the international study group of liver surgery. Surgery 2011;149:680e8.
16. Fegrachi S, Besselink MG, Van Santvoort HC, Van Hillegersberg R, Molenaar IQ Radiofrequency ablation for unresectable locally advanced pancreatic cancer:a systematic review. Hpb 2014;16:119e23.
17. Kneuertz PJ, Cunningham SC, Cameron JL, Torrez S, Tapazoglou N, Herman JM, et al. Palliative surgical management of patients with unresectable pancreatic adenocarcinoma: trends and lessons learned from a large, single institution experience. J Gastrointest Surg 2011;15:1917e27.
18. Tweel I Van Der. Sample size determination. 2006.
19. Wu Y, Tang Z, Fang H, Gao S, Chen J, Wang Y, et al. High operative risk of cooltip radiofrequency ablation for unresectable pancreatic head cancer. J Surg Oncol 2006;94:392e5.
20. Girelli R, Frigerio I, Salvia R, Barbi E, Tinazzi Martini P, Bassi C. Feasibility and safety of radiofrequency ablation for locally advanced pancreatic cancer. Br J Surg 2010;97:220e5.
21. Van Wagensveld BA, Coene PPLO, Van Gulik TM, Rauws EAJ, Obertop H, Gouma DJ. Outcome of palliative biliary and gastric bypass surgery for pancreatic head carcinoma in 126 patients. Br J Surg 1997;84:1402e6.

22. Heinicke JM, Büchler MW, Laffer UT. Bilio-digestive double bypass for nonresectable pancreatic cancer. Dig Surg 2002;19:165e7.
23. Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as firstline therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997;15:2403e13.
24. Cantore M, Girelli R, Mambrini A, Frigerio I, Boz G, Salvia R, et al. Combined modality treatment for patients with locally advanced pancreatic adenocarcinoma.Br J Surg 2012;99:1083e8.
25. Giardino A, Girelli R, Frigerio I, Regi P, Cantore M, Alessandra A, et al. Triple approach strategy for patients with locally advanced pancreatic carcinoma. Hpb 2013;15:623e7.
26. Seicean A, Tefas C, Ungureanu B, Săftoiu A. Endoscopic ultrasound guided radiofrequency ablation in pancreas. Hepatogastroenterology 2014;61:1717e21.
27. D'Onofrio M, Crosara S, De Robertis R, Butturini G, Salvia R, Paiella S, et al. Percutaneous radiofrequency ablation of unresectable locally advanced pancreatic cancer: preliminary results. Technol Canc Res Treat 2017;16:285e94.
28. Rombouts SJ, Walma MS, Vogel JA, van Rijssen LB, Wilmink JW, Mohammad NH, et al. Systematic review of resection rates and clinical outcomes after FOLFIRINOX-based treatment in patients with locally advanced pancreatic cancer. Ann Surg Oncol 2016;23:4352e60.
29. Suker M, Beumer BR, Sadot E, Marthey L, Faris JE, Mellon EA, et al. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. Lancet Oncol 2016;17:801e10.
30. Dutch Trial registry. PELICAN trial: local ablative treatment of an inoperable pancreas carcinoma.Trial ID: NTR 5517. Available at: www.trialregister.nl [n.d].

Chapter 10

Radiofrequency ablation and chemotherapy versus chemotherapy alone for locally advanced pancreatic cancer (PELICAN): study protocol for a randomized controlled trial

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ABSTRACT

Background

Approximately 80% of patients with locally advanced pancreatic cancer (LAPC) are treated with chemotherapy, of whom approximately 10% undergo a resection. Cohort studies investigating local tumor ablation with radiofrequency ablation (RFA) have reported a promising overall survival of 26-34 months when given in a multimodal setting. However, randomized controlled trials (RCTs) investigating the effect of RFA in combination with chemotherapy in patients with LAPC are lacking.

Methods

The 'Pancreatic Locally Advanced Unresectable Cancer Ablation' (PELICAN) trial is an international multicenter superiority RCT, initiated by the Dutch Pancreatic Cancer Group (DPCG). All patients with LAPC according to DPCG criteria, who start with FOLFIRINOX or (nab-paclitaxel/)gemcitabine are screened for eligibility. Restaging is performed after completion of four cycles of FOLFIRINOX or two cycles of (nab-paclitaxel/)gemcitabine (i.e. two months of treatment) and results are assessed within a nationwide online expert panel. Eligible patients with RECIST stable disease or objective response, in whom resection is not feasible, are randomized to RFA followed by chemotherapy or chemotherapy alone. In total, 228 patients will be included in 16 centers in the Netherlands and four other European centers. The primary endpoint is overall survival. Secondary endpoints include progression free survival, RECIST response, CA 19.9 and CEA response, toxicity, quality of life, pain, costs and immunomodulatory effects of RFA.

Discussion

The PELICAN RCT aims to assess whether the combination of chemotherapy and RFA improves overall survival when compared to chemotherapy alone, in patients with LAPC with no progression of disease following two months of systemic treatment.

Trial registration

The trial was registered in the Dutch Trial Registry on December 29th, 2015 and at clinicaltrials.gov on October 1st, 2018 (www.trialregister.nl, Trial ID: NL4997, www.clinicaltrials.gov, NCT03690323 retrospectively registered).

BACKGROUND

Pancreatic cancer is among the most deadliest of cancers with a worldwide incidence of approximately 460,000 new cases and 430,000 deaths in 2018.[1] Approximately 80-90% of patients have no curative options due to metastatic disease or local tumor invasion into adjacent structures, i.e. locally advanced pancreatic cancer (LAPC).[2,3] Unfortunately, treatment options for patients with LAPC are limited. In patients with advanced pancreatic cancer, systemic treatment with gemcitabine monotherapy was found to improve quality of life compared to 5-FU and resulted in a median survival of 10-12 months in patients with LAPC.[4-6] FOLFIRINOX (a combination of 5-fluorouracil, oxaliplatin, irinotecan and leucovorin) as well as nab-paclitaxel/gemcitabine showed a four- and two-month survival benefit respectively, compared to gemcitabine monotherapy in patients with metastatic pancreatic cancer.[7,8] Although no randomized controlled trials (RCTs) were performed, in patients with LAPC, both chemotherapy regimens have become generally accepted as standard treatment in these patients.[9] Observational studies report an overall survival, according to intention to treat analyses, of 24 months for selected patients with LAPC after FOLFIRINOX and 19 months with nab-paclitaxel/gemcitabine.[10,11]

The first study on radiofrequency ablation (RFA) in patients with pancreatic cancer was published in 2000.[12] RFA is a thermal-based local ablative therapy aiming for tumor destruction through application of a high frequency alternating current through one or more electrodes implanted into the tumor.[13] The principle of RFA for pancreatic cancer is essentially a form of tumor debulking rather than total tumor ablation, since several nearby vital structures are at risk. Overall complications and mortality were reported in 26% and 3% respectively, after developing a method that leaves a peripheral rim of tumor as a safety margin to surroundig tissues.[14] Since then, several non-randomized studies have demonstrated RFA to be feasible and safe.[15,16] When RFA was performed in a multimodal setting, combined with chemo(radio)therapy, a promising survival of 26–34 months was reported from single center observational studies.[17] To objectively establish a survival benefit for RFA in LAPC in the current era of improved chemotherapy regimens, a RCT is needed.

Aim

The 'Pancreatic Locally Advanced Unresectable Cancer Ablation (PELICAN)' trial aims to compare median overall survival after a combination of chemotherapy with RFA versus chemotherapy alone, in patients with LAPC.

OBJECTIVES AND METHODS

The study objectives are to:

- Determine whether the combination of RFA and chemotherapy improves overall survival for patients with LAPC, compared to chemotherapy alone
- Determine the effect of RFA combined with chemotherapy on pain, disease progression, tumor markers and quality of life
- Evaluate complications of RFA as well as toxicity of chemotherapy and to estimate costs of both treatment arms.

Study design

The PELICAN trial is an international multicenter parallel-group superiority RCT, initiated by the Dutch Pancreatic Cancer Group (DPCG).

Study population

All patients with LAPC according to the National Comprehensive Cancer Network (NCCN) criteria (Table 1), without progression of disease who completed four cycles of FOLFIRINOX or two cycles of (nab-paclitaxel/)gemcitabine, and are technically eligible for RFA will be screened for study eligibility.[18] In addition, those patients with NCCN borderline resectable disease after chemotherapy, based on preoperative imaging, who are found to be unresectable during explorative laparotomy due to local extension of disease, will be eligible for study inclusion.

Table 1. Definitions of the National Comprehensive Cancer Network (NCCN) and Dutch Pancreatic Cancer Group (DPCG) for locally advanced pancreatic cancer

	Arterial involvement	Venous involvement
NCCN criteria	SMA and celiac trunc involvement>180°, aortic involvement	Unreconstructable PV/SMV occlusion
DPCG criteria	SMA, celiac trunc or hepatic artery involvement >90°	PV/SMV involvement >270° or occlusion

NCCN, National Comprehensive Cancer Network; DPCG, Dutch Pancreatic Cancer Group; SMA, superior mesenteric artery; PV, portal vein; SMV, superior mesenteric vein.

Eligibility

Inclusion criteria are as follows:

- Age ≥18 years
- Histologically or cytologically confirmed or suspected pancreatic ductal adenocarcinoma
- Locally unresectable tumor based on imaging according to NCCN criteria, or unresectable during explorative laparotomy
- Stable disease or partial response after four cycles of FOLFIRINOX or two cycles of (nab-paclitaxel/)gemcitabine (i.e. two months of treatment), according to Response Evaluation Criteria in Solid Tumors v1.1 (RECIST) [19] and evaluated by the expert panel
- Fit for surgery assessed by the treating surgeon and anesthesiologist
- Fit for chemotherapy as assessed by the medical oncologist, plus:
  - Absolute neutrophil count ≥1.5 × 109/L
  - Platelet count ≥100 × 109/L
  - Renal function: creatinine clearance > 50 ml/min
  - AST/ALT ≤ 3 x the upper limit of normal
- RFA must be technical feasible (Additional file 1), assessed by an interventional radiologist from the expert panel
- Written informed consent

Exclusion criteria are as follows:

- World Health Organization (WHO) performance status ≥3
- Distant metastases on abdominal or thoracic computed tomography (CT) scan
  - Lymph nodes are considered distant metastases according to the International Study Group of Pancreatic Surgery, and only when pathologically proven[20]
- Previous surgical resection, local ablative, radio- or chemotherapy for pancreatic cancer, other than the protocolled four cycles FOLFIRINOX or two cycles (nab-paclitaxel/)gemcitabine
- A concomitant stenosis of >50% of the hepatic artery and the portal or superior mesenteric vein
- A second primary malignancy, except adequately treated non-melanoma skin cancer, in situ carcinoma of the cervix uteri or other malignancies treated at least 5 years previously without signs of recurrence
- Pregnancy

Registration and randomization

Figure 1 shows the trial flow diagram. Patients will be identified for potential eligibility during the multidisciplinary team meeting at diagnosis. All patients with LAPC, based upon imaging, according to DPCG criteria (Table 1) will be asked for informed consent for registration by a study coordinator, research nurse or principal investigator. Patients will be treated in accordance with standard of care and will either start chemotherapy or best supportive care, based on the advice of the multidisciplinary team meeting and shared decision-making between patient and a medical LAPC, locally advanced pancreatic cancer; MDT, multidisciplinary team; CT, computed tomography; RECIST, response evaluation criteria in solid tumors; RFA, radiofrequency ablation, NCCN, national comprehensive cancer network oncologist. In case of jaundice, patients will preferably receive a covered metal stent prior to induction therapy.[21] Patients who complete four cycles of FOLFIRINOX or two cycles of (nab-paclitaxel/)gemcitabine will be restaged with a CT-scan of chest and abdomen according to a standardized biphasic contrast-enhanced protocol. A nationwide expert panel consisting of abdominal radiologists, pancreatic surgeons and interventional radiologists will review all restaging CT-scans to evaluate response to chemotherapy (RECIST v1.1), potential surgical resectability (NCCN criteria) and technical eligibility for RFA (Additional file 1).[18,19] Patients with progressive disease and those patients that are not technical eligible for RFA as determined by the expert panel are excluded. Patients who will be determined as borderline resectable at restaging, according to the NCCN guidelines, will undergo an explorative laparotomy with the intention for curative resection. If the tumor is found to be locally unresectable during surgery, the patient will be randomized intra-operatively for either RFA plus chemotherapy or chemotherapy alone. Prior to the explorative laparotomy, all patients must have provided written informed consent. The majority of patients, however, will be the group with NCCN unresectable, stable disease at restaging. The latter category of patients will be randomized at the outpatient clinic after obtaining written informed consent. Randomization will be performed centrally using a computer generated randomization schedule randomization module (ALEA, Clinical Research Unit) in a 1:1 ratio between:

- Intervention-arm: RFA during laparotomy followed by continuation of chemotherapy
- Control-arm: Direct continuation of pre-randomization chemotherapy

Randomization will be stratified by institute and chemotherapy regimen.

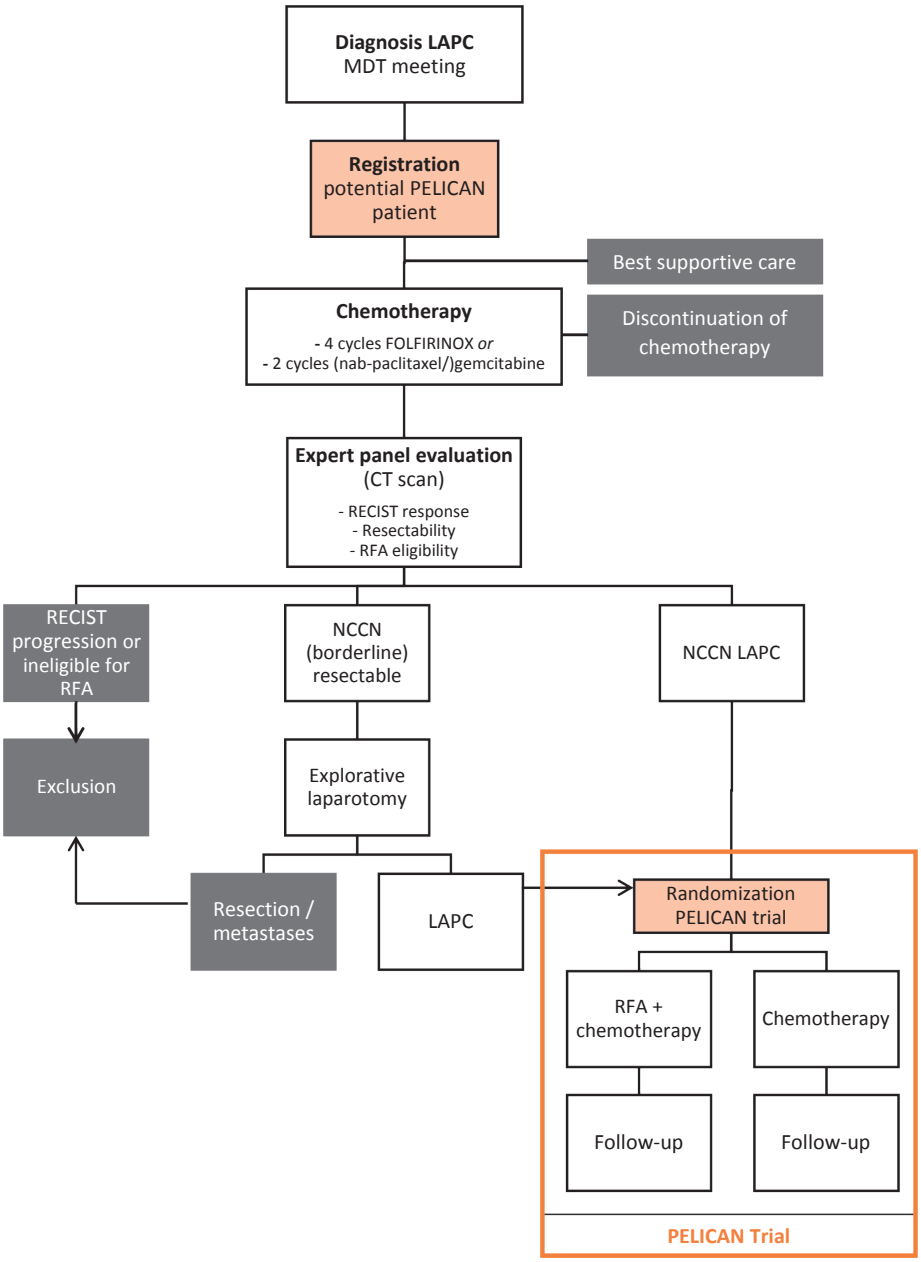

Figure 1. Trial flow diagram

Intervention: radiofrequency ablation

Patients will be scheduled for surgery within four weeks after the restaging CT-scan. All patients will receive antibiotic prophylaxis to prevent surgical site infections (cefazolin 2g/metronidazole 500mg) and will be administered a long-acting analogue of somatostatin. The surgical procedure will be started with an exploratory laparoscopy to evaluate the presence of liver or peritoneal metastases. When there are no pathologically confirmed metastases, in the same session a median laparotomy will be performed. The pancreas will be exposed by Kocher maneuver. In case a tumor appears to be resectable during exploration and/or intra-operative ultrasound, conversion to a resection will be performed. When LAPC is confirmed intra-operatively, a cold wet gauze will be placed over the vena cava to prevent potential thermal damage. When a metal stent was placed during the preoperative period, this is preferably removed first. Then, a RFA probe will be positioned by the interventional radiologist under direct ultrasound guidance, taking into account a prescribed safety zone to vital structures aiming for maximal tumor debulking rather than total tumor ablation (Additional file 1). A tumor biopsy will be taken intra-operatively from the center of the tumor, before and after RFA, as well as blood samples to measure immunomodulatory factors. RFA will be carried out with the multipolar CelonLab® POWER System generator, Celon Aquaflow® and bipolar Celon-ProSurge® (micro) applicators with exposure lengths of 9/15/20/30/40mm (Olympus Surgical Technologies Europe, Teltow, Germany). A total of 15 kJ per probe will be delivered with a power setting of 1W per mm probe length for probes 20-40mm and 0.5 and 0.9kJ with a power of 3 and 5W for 9 and 15mm probes respectively.[16,22-24] During RFA, the duodenum will be continuously perfused with cold saline through two nasogastric tubes to prevent thermal damage. One outflow-tube will be placed directly post pyloric, whereas the inflow-tube will be placed in the duodenum near the ligament of Treitz to ensure a continuous duodenal flow with cold saline. A bowel clamp will be placed at the proximal jejunum to prevent cold saline to flow towards the ileum. RFA will be followed by a hepaticojejunostomy in all cases of a pancreatic head tumor. In case of expected duodenal obstruction a gastric bypass (gastrojejunostomy) will be performed. An abdominal drain will be placed within the omental bursa and the abdomen will be closed. After surgery, patients will be treated for four weeks with omeprazole 40mg and thrombosis prophylaxis. Amylase will be measured from the drain fluid at day 1 and day 3 and a biphasic CT-scan of the abdomen will be performed 7 days after the RFA procedure to visualize the RFA effect and to have a baseline scan before restarting chemotherapy. The additional chemotherapy schedule will be resumed as soon as patients are recovered from the RFA procedure.

Control: chemotherapy alone

Patients will continue the chemotherapy treatment which was started after diagnosis, based on the advice of the multidisciplinary team meeting and shared decision-making

between patient and a medical oncologist. In general patients with a WHO performance status 0-1 and serum bilirubin levels ≤1,5 times the upper limit of normal value will receive FOLFIRINOX or nab-paclitaxel/gemcitabine. If these criteria are not met, mostly nab-paclitaxel/gemcitabine or gemcitabine monotherapy will be administered. The objective is to administer a further 8 cycles of FOLFIRINOX after randomization or a further 4 cycles of (nab-paclitaxel/)gemcitabine. Details on chemotherapy administration are described in Additional file 2.

During chemotherapy response evaluation with biphasic CT-scans of chest and abdomen will be performed after every four cycles of FOLFIRINOX or every two cycles of (nab-paclitaxel/)gemcitabine (i.e. two months).

Study endpoints and definitions

The primary endpoint is overall survival by intention to treat, defined as the period of time between randomization and death by any cause. Patients alive at last follow-up will be (right-)censored. Secondary endpoints are progression free survival and radiologic tumor response according to RECIST v1.1, CA 19.9 and CEA response, toxicity according to National Cancer Institute (NCI) Common Terminology Criteria (CTC) for adverse events v 4.0, quality of life (QLQ-C30, PAN-26), pain (visual analogue scale), immunomodulatory effects (TNF-a, IL-8, IL-1-a, IL-1-b, MCP-1, IL-6, IL-33, DAMPs and phenotyping) and costs.[19,25-27] Progression free survival is defined as the period of time between randomization and the date of local/regional progression, established on CT-imaging, or occurrence of distant metastases or occurrence of a second pancreatic cancer or death.[28] Patients will be censored if a new anti-cancer therapy will be started prior to documented progression or if two or more response assessments will be missed prior to a visit which documented progression. In the RFA-arm, postoperative complications are scored according to International Study Group of Pancreatic Surgery.[29-32]

Data collection and follow-up

The selection of patients included in the trial will be made transparent by collecting reason for ineligibility for all registered patients with diagnosis LAPC that are excluded during trial workup. After trial inclusion, baseline characteristics will be collected using standardized case record forms comprising age, sex, medical history, tumor markers, laboratory results, pre-randomization treatment, tumor characteristics (tumor size, location, vascular involvement), response to treatment, WHO performance status, body mass index, pain (visual analogue scale) and quality of life. Treatment characteristics include chemotherapy dosage, modifications including reasons, toxicity, RFA procedural details (e.g. number of probes, distance to vital structures on intra-operative ultrasound,

power settings, bypass surgery) and postoperative time to discharge and complications. After randomization patients will be followed up at 1, 3, 6, 12 and 18 months after start of the study treatment (i.e. date of RFA in group A and date of continuation of chemotherapy in group B). The follow up consists of medical history including pain scores and WHO performance status, laboratory values (including tumor markers) and quality of life questionnaires. Furthermore, during chemotherapy a biphasic CT-scan of chest and abdomen will be performed every two months for response evaluation. After completion of chemotherapy, CT-scans will only be performed when indicated (i.e. complaints). See Figure 2 for a schedule of data collection and follow-up according to SPIRIT recommendations.[33] Due to the nature of the intervention neither participants nor staff can be blinded to allocation.

		STUDY PERIOD								
		Enrolment		**Allocation**	**Post-allocation**					**Close-out**
	TIMEPOINT	**Diagnosis**	**+2 months of therapy**	**0**	**RFA**	**postop**	**Every CTx cycle**	**Every two months during CTx**	**Follow-up (1, 3, 6, 12, 15, 18 months)**	**18 months post-intervention**
ENROLMENT	Registration	X								
	Expert panel		X							
	Eligibility screen		X							
	Informed consent		X							
	Allocation			X						
INTERV	RFA and Chemotherapy				X		X			
	Chemotherapy						X			
ASSESSMENTS	Baseline characteristics		X							
	CT-scan		X			X		X		
	Tumor markers	X	X			X			X	X
	Intra-operative biopsy + outcomes				X					
	Post-operative complications					X				
	(Progression free) survival status								X	X
	WHO status	X	X				X		X	X
	VAS pain scores	X	X		X	X	X		X	X
	Toxicity + laboratory investigation		X			X	X		X	X
	QoL-C30 & PAN26		X						X	X

Figure 2. Schedule of enrolment, interventions and assessments according to SPIRIT guidelines

Quality and safety

All participating centers that will perform RFA must have an available interventional radiologist or surgeon who routinely applies ultrasound guided RFA procedures (e.g. for liver tumors).[34] Furthermore, all participating centers had perform pancreatic surgery.[35] To ensure the quality of the implementation of RFA pancreas, a RFA-workshop was organized by the UMC Utrecht and Amsterdam UMC prior to the start of the study, during which specialists received a hands on training in the execution of RFA procedures by proctors from Verona during two surgical procedures. Furthermore, in each participating hospital at least the first two RFA procedures will be performed in the presence of an interventional radiologist of the trial's expert panel. The exact frequency of the proctored procedures will be tailored based on the local expertise as assessed by the experienced proctor together with the participating center.

All (serious) adverse events ((S)AE) up to 28 days after the last protocol treatment will be recorded, except those directly related to progression of disease. SAEs will be reported to the principal investigator within 24 hours, and within 15 days to the accredited medical ethical committee that approved the protocol. When a SAE results in death, it will be reported within 7 days after notification. (S)AEs will be reported through a web portal to the central committee on research involving human subjects (CCMO) and the accredited institutional review board.

In order to ensure the quality of the study, data collection and study monitoring will be performed by an independent research agency: the IKNL clinical research department. Pre-defined case report forms can be found at www.dpcg.nl/studie/pelican-2. The study monitor will have full access to the data to monitor the progress of the trial, captured and reported data and to monitor the implementation in accordance with the protocol and good clinical practice (GCP) standards. The monitoring plan includes: verification of informed consent documents, checking in- and exclusion criteria for the first 10 patients per center and 25% afterwards; source data verification of 25% of included patients; regular on-site monitoring (twice a year per center, depending on patient enrollment); checking adverse events in 10-25% of cases; and verification of essential documents within the investigator site file. Within each center a local data manager is placed, responsible for including data within an electronic web-based database, query response and communication with the central study monitor.

An independent data safety monitoring board (DSMB) consisting of at least a statistician or epidemiologist, surgeon and gastroenterologist will monitor the safety of the trial subjects. Safety analyses will be held after each 20% of the sample size has completed the follow up period. One formal interim analyses for efficacy will be performed after

85 events (i.e. death from any cause). The advice of the data safety monitoring board meeting will be shared with the steering committee and the ethical board of the trial.

Sample size

Randomized controlled trials in patients with LAPC reported an average median survival of 10.4 months for patients receiving gemcitabine.[5,6,36] During the design of the study (2014), literature on FOLFIRINOX and nab-paclitaxel/gemcitabine only including patients with metastatic disease and described a survival of 11.1 and 8.5 months respectively.[7,8] A three month survival difference was seen for patients treated with gemcitabine monotherapy when comparing LAPC with metastatic disease.[5-8,36] This difference was extrapolated to LAPC patients treated with FOLFIRINOX and nab-paclitaxel resulting in an estimated survival of 14.1 and 11.5 months after FOLFIRINOX and nab-paclitaxel/gemcitabine respectively. Taking into account that FOLFIRINOX was expected to be the most prescribed regimen, and taken into account an estimated time of 2-3 months between start of chemotherapy and randomization, a survival of 10.2 months from randomization was estimated for the control group. Regarding the experimental study arm, a median survival benefit of at least 5.5 months with RFA + chemotherapy treatment was considered clinically worthwhile. Considering time from randomization, this would translate into a median survival of 15.7 months, corresponding to a hazard ratio of 0.65. In order to have 80% power to detect a 35% reduction in the risk of death if RFA is added to chemotherapy, with a 1-sided 2.5% trial-wise type I error rate, a total of 169 events (death of any cause) need to be observed. Assuming a 2-year patients accrual period and a final analysis after another 18 months a total of 228 patients need to be randomized in a 1:1 ratio, allowing an interim analysis after approximately half (1/2) of the total number of events.

Statistical analysis

All randomized patients will be included in the analysis of overall survival and progression free survival, according to the intention-to-treat principle. The final analysis on overall survival will be performed after having observed 169 events at about 42 months at a 2.45% 1-sided significance level, adjusted for the interim analysis. In addition, a per protocol analyses will be performed. Kaplan-Meier curves for proportions of event-free patients in each treatment arm will be calculated. The 95% confidence intervals for the median of time to event endpoints will be computed using the method of Brookmeyer and Crowley. In the primary analysis, the two treatment arms will be compared using the log-rank test stratified by the stratification factor except center. Treatment effect and its 95% confidence interval will be estimated from Cox regression model, stratified by the stratification factor except center. In addition, the effect of study center and other potential prognostic factors, such as location of the tumor on overall

survival will be assessed using Cox regression. The Schoenfeld residual plots will be used to check the model assumption for the Cox regression.

Secondary outcomes will be examined using descriptive statistics, using mean with standard deviation or median with interquartile range when appropriate for continuous data and number with percentage for categorical data. Comparison between groups will be done with chi-square tests and independent sample t-tests when appropriate. Changes of the quality of life scores while on treatment versus baseline will be examined on specific time points to explore treatment side effect on patients QoL and the longtime benefit of the study treatment. Baseline scores will be compared using a Wilcoxon rank sum test, and a pattern mixture model identifying drop-out patients as a special category, will be performed to evaluate the effect of missing data.[37]

Premature termination of the study

Based on the Lan-DeMets error spending function with O'Brian-Fleming type of boundaries, a significant benefit from RFA with chemotherapy is claimed if a p-value of less than 0.00153 in favor of RFA with chemotherapy will be observed at the interim analysis. Furthermore, an independent data safety monitoring board will analyze safety and may advise the trial steering committee to adjust or stop the study prematurely in case of safety concerns, taking study outcome into account.

Modification of the protocol

Any modifications to the protocol which may impact on the conduct of the study, potential benefit or safety of the patient, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Additional file 3 includes all amendments until July 2020 that were all approved by the Ethics Committee prior to implementation.

Dissemination policy

The trial results will be submitted for presentation at (inter)national conferences (i.e. International Hepato-Pancreato-Biliary Association (IHPBA), The Americas HPBA (AHPBA), European-African HPBA (E-AHPBA), European Pancreatic Club, Pancreas Club Annual Meeting) and publication in a peer-reviewed journal, regardless of the outcome. When positive trial result will be established, other centers that perform pancreatic surgery will be proctored by interventional radiologists from the PELICAN expert panel. Extensive experience with proctoring in national and international centers within the trial has already been gained. Moreover, RFA of the pancreas should only be implemented in centers that routinely apply ultrasound guided RFA procedures (e.g. for liver tumors).

Co-authorship will be based on the international ICMJE guidelines, with at least one co-authorship per site (internally determined) and more depending on the inclusion rate. Furthermore, all the members of the protocol writing committee will be awarded with an authorship after revising the work critically, since they substantially contributed to the conception and design of this study.

DISCUSSION

The PELICAN trial is an international multicenter randomized controlled superiority trial designed to assess whether in patients with LAPC, RFA in combination with chemotherapy improves overall survival as compared with chemotherapy alone.

In preparation for the trial, surgeons and interventional radiologists of the principal study sites were trained by the expert group in Verona, including a visit in Italy and on-site proctoring in the Netherlands. Afterwards, the study group performed two experimental studies and a phase II clinical safety study to assess safety and the effect of the RFA settings.[16,23,24] As described in the methods section, an extensive proctoring plan was designed, to further secure the quality and safety of the study procedure. With these results and measures, it was decided together with the Dutch Pancreatic Cancer Group (DPCG) that a randomized controlled phase III trial was justified and safe and the PELICAN trial was designed.

During the design phase of the PELICAN trial, the timing of restaging within the expert panel and consideration for trial inclusion as well as explorative laparotomy was a matter of debate. In earlier days, when standard treatment for patients with LAPC was gemcitabine monotherapy, most studies performed RFA as upfront therapy.[14,16] However, in the current era of FOLFIRINOX, a more pronounced improvement of overall survival and also the possibility of a resection after chemotherapy are described.[38,39] In addition, studies that investigated RFA as part of a multimodal treatment strategy showed improved overall survival up to 34 months.[40] Therefore, it was decided to investigate the effect of RFA only after a period with one of the standard chemotherapy regimens. Based on consensus meetings and a survey among the participating medical oncologists it was decided to include patients after the first response evaluation after approximately two months of treatment. It was expected that drop-out due to toxicity was minimal at this moment. This was also consistent with the largest published cohort at that moment where 75% of consolidation therapy was started after the first tumor evaluation.[41] Current studies focusing on resection after induction chemotherapy mostly advice a period of four to six months before proceeding to a surgical explorative laparotomy,

which is longer than defined in the PELICAN trial protocol. This might suggest, that patients included in the trial, are withheld a possible surgical resection. However, we do not yet know the ideal timing of an explorative laparotomy since these advices are all based on expert opinions. Also, after inclusion in the trial, patients will receive response evaluations with a CT-scan every two months and can proceed to a surgical exploration even after randomization within the study.[9] This might introduce bias when an imbalance between resections will arise between treatment arms. This can also result from the explorative laparotomy in advance of the RFA procedure, in which patients might undergo a resection. In order to minimize this bias, patients with potential resectable disease are randomized intra-operatively, after unresectability has been established. Moreover, a per protocol analysis and Cox regression analysis will be done to investigate and eliminate this potential effect on overall survival.

During design of the study, it was discussed whether a staging laparoscopy for all patients prior to randomization was needed, since occult metastases are present in up to 19% of patients with LAPC and these patients are not eligible for radiofrequency ablation.[42] However, since patients are included after induction chemotherapy it is uncertain whether these metastases will be detectable. Moreover, within the control arm, it would have no consequences when occult metastases will be found. Therefore, it was decided as unethical to perform an invasive procedure without consequences in at least 50% of patients (control arm). It can be assumed that due to randomization, patients with occult metastases are equally distributed between groups. Since, results will be analyzed according to the intention-to-treat principle, this bias will influence both groups equally. In recently published studies, the median overall survival of patients with LAPC treated with FOLFIRINOX seems longer than 14.1 months as assumed during the sample size calculation. A recent meta-analysis reported a median overall survival of 24 months for patients with LAPC treated with (modified) FOLFIRINOX.[11] Although it was taken into account that the population included within the trial will be a favorable selection of patients, this suggests an underestimated survival within the control arm. If true, this results in an underpowered study with the current sample size. However, the studies included within the meta-analysis are mostly single center studies from experienced centers and also included patients receiving FOLFIRINOX as multimodal treatment strategy in combination with a resection or (chemo) radiotherapy.[38,43,44] Different definitions for LAPC are used and the external validity of these results is uncertain. A recent observational study including 680 consecutive patients with borderline resectable and LAPC showed a median overall survival of 13 months for all patients after an intention-to-treat analysis.[45] Recent multicenter data from the Netherlands showed a median overall survival of 14 months for patients with LAPC treated with FOLFIRINOX.[46] These studies likely better reflect 'real-world' data and the assumption of 14.1 months can be preserved with these data.

Obviously, due to the nature of the study with a non-surgical control arm and a surgical intervention it is impossible to blind patients and treating physicians. Therefore, performance and ascertainment bias might be introduced for subjective secondary outcomes like quality of life, pain scores and these results must thus be interpreted with care. Furthermore, a practical issue that will be challenging, is the multicenter nature of the study combined with the pre-randomization registration in which many potential patients need to be followed in order to include only those that are eligible. Other pending randomized controlled trials that investigate ablative treatment strategies in patients with LAPC are the CROSSFIRE trial (clinicaltrials.gov NCT02791503), DIRECT trial (clinicaltrials.gov NCT03899649) and the PANC0015 trial (clinicaltrials.gov NCT01926197). The latter is the only other registered study that compares an ablative therapy directly with chemotherapy in a randomized setting and inclusion currently stopped due to low accrual. This affirms the difficulty of performing a randomized controlled trial within this specific patient population and emphasizes the importance to perform this trial with a large multicenter collaboration like the Dutch Pancreatic Cancer Group.[47] Within this multidisciplinary organization there is a lot of experience with multicenter studies and together with a data management grant from the Dutch Cancer Society we are confident that we will have enough resources to manage the trial and complete it successfully.

Trial status

The first patient was randomized on 7 April 2015. At the time of protocol submission (July 2020), protocol version 10.2 (6 March 2018) was effective and 16 centers in the Netherlands and 3 centers in Belgium and Spain were actively recruiting patients for the trial. 149/228 patients (65%) have been randomized. See www.dpcg.nl/studie/pelican-2 for up to date information on participating centers and number of included patients. Inclusion is behind schedule which is partly related to a higher than expected proportion of patients undergoing surgical resection with curative intent and more patients than expected being ineligible for RFA. This was discussed within the Medical Ethical Committee and Data Safety Monitoring Board and Grant provider (Dutch Cancer Society) in 2017 and 2018. Since the PELICAN trial is the only ongoing randomized controlled trial worldwide on this specific topic, all acknowledged the importance of the trial. To improve patient accrual, 3 more centers in Europe were opened for inclusion. It is estimated that recruitment will be completed in December 2021.

DECLARATIONS

Ethics approval and consent to participate

The study is performed in accordance with the declaration of Helsinki. Furthermore, the study is done in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO) and the 93/42/EEC European Medical Device Directive. The protocol has been approved by the Medical Ethical Committee of the Academic Medical Centre (reference number: 2015_325, 24 December 2014; contact: mec@amsterdamamc.nl), secondary approval was obtained from all participating centers individually. Patients are only eligible for inclusion after written informed consent. All patient information and informed consent forms are approved by the Institutional Review Board. The trial is registered in the Dutch Trial Registry (www.trialregister.nl, Trial ID: NTR 5517) and within clinicaltrials.gov (NCT03690323).

SPIRIT guidelines

The PELICAN trial protocol was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT). The SPIRIT checklist has been included as Additional file 4. The SPIRIT figure is Figure 2.

Competing interests

JWdG has received personal fees outside the submitted work from Bristol-Myers Squibb, Roche, Pierre-Fabre, Servier, MSD, Novartis; RvH is a proctor for Intuitive, is part of the advisory board of Medtronics and received an educational grant from Olympus outside the submitted work; IdH reports grants from Roche Pharmaceutical , QPS/RanD, and Medtronic, outside the submitted work; KvL reports personal fees and non-financial support from AngioDynamics, outside the submitted work; VEdM reports grants from Stichting Louise Vehmeijer and NWO and travel grants from Astellas, and from Neovii, outside the submitted work; MRM reports grants, personal fees and non-financial support from Angiodynamics, grants and personal fees from Medtronic Covidien, and non-financial support from Cascination, outside the submitted work.; NHM reports advisory board fees for her institution from BMS, Eli Lilly, Servier, and MSD; JdVG reports grants and non-financial support from Servier, outside the submitted work; JWW reports research grants from Servier, Halozyme, Novartis, Celgene, Astra Zeneca, Pfizer, Roche, Amgen, Merck and a consulting/advisory role for Servier and Celgene; HCvS has received a research grant from the Dutch Cancer Society, during and outside the submitted work; MGB has received a research grant from the Dutch Cancer Society during and outside the conduct of the study. IQM has received a research grant from the Dutch Cancer Society during the conduct of the study. For all other authors, there are no conflicts of interest.

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Authors' contributions

IQM, MGB and HvS are the principal investigators of the trial. They conceived the study, led the proposal and protocol development. MSW, SJR and LB drafted the manuscript. MSW, SJR, LJHB, IHBR, KB, RCB, ORB, GJC, FD, RMvD, OMvD, SF, PG, DJdG, JWdG, NHM, RvH, IHdH, MDH, EDK, MSvL, MSL, KPvL, ML, VEdM, MRM, LJM, CYN, IOA, EP, GAP, MBP, JFP, GR, JAR, MWJS, JdVG, JJdV, EMvdW, FJW, JWW, HCvS, MGB and IQM participated in the design of the trial and the study proposal. SJR, MSW and LB primarily coordinate the trial. All authors critically reviewed the manuscript, approved the final version, and are fully aware of this publication.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin [Internet]. 2018;68:394–424. Available from: http://doi.wiley.com/10.3322/caac.21492
2. Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. Lancet. 2011;378:607–20.
3. Latenstein AEJ, van der Geest LGM, Bonsing BA, Groot Koerkamp B, Haj Mohammad N, de Hingh IHJT, et al. Nationwide trends in incidence, treatment and survival of pancreatic ductal adenocarcinoma. Eur J Cancer. 2020;125:83–83.
4. Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first- line therapy for patients with advanced pancreas cancer: A randomized trial. J Clin Oncol. 1997;15:2403–13.
5. Louvet C, Labianca R, Hammel P, Lledo G, Zampino MG, André T, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: Results of a GERCOR and GISCAD phase III trial. J Clin Oncol. 2005;23:3509–16.
6. Lima CMR, Green MR, Rotche R, Miller WH, Jeffrey GM, Cisar LA, et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. J Clin Oncol. 2004;22:3776–83.
7. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364:1817–25.
8. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013/10/18. 2013;369:1691–703.
9. van Veldhuisen E, van den Oord C, Brada LJ, Walma MS, Vogel JA, Wilmink JW, et al. Locally Advanced Pancreatic Cancer: Work-Up, Staging, and Local Intervention Strategies. Cancers (Basel). 2019;11:976.
10. Philip PA, Lacy J, Portales F, Sobrero A, Pazo-Cid R, Manzano Mozo JL, et al. Nab-paclitaxel plus gemcitabine in patients with locally advanced pancreatic cancer (LAPACT): a multicentre, open-label phase 2 study. Lancet Gastroenterol Hepatol. 2020;5:285–94.
11. Suker M, Beumer BR, Sadot E, Marthey L, Faris JE, Mellon EA, et al. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. Lancet Oncol [Internet]. Elsevier Ltd; 2016;17:801–10. Available from: http://dx.doi.org/10.1016/S1470-2045(16)00172-8
12. Matsui Y, Nakagawa A, Kamiyama Y, Yamamoto K, Kubo N, Nakase Y. Selective thermocoagulation of unresectable pancreatic cancers by using radiofrequency capacitive heating. Pancreas. 2000;20:14–20.
13. Mirza AN, Fornage BD, Sneige N, Kuerer HM, Newman LA, Ames FC, et al. Radiofrequency ablation of solid tumors. Cancer J. 2001;7:95–102.
14. Girelli R, Frigerio I, Giardino A, Regi P, Gobbo S, Malleo G, et al. Results of 100 pancreatic radiofrequency ablations in the context of a multimodal strategy for stage III ductal adenocarcinoma. Langenbeck's Arch Surg. 2013;398:63–9.
15. Girelli R, Frigerio I, Salvia R, Barbi E, Tinazzi Martini P, Bassi C. Feasibility and safety of radiofrequency ablation for locally advanced pancreatic cancer. Br J Surg. 2010;97:220–5.
16. Fegrachi S, Walma MS, de Vries JJJ, van Santvoort HC, Besselink MG, von Asmuth EG, et al. Safety of radiofrequency ablation in patients with locally advanced, unresectable pancreatic cancer: A phase II study. Eur J Surg Oncol. 2019;45:2166–72.
17. Cantore M, Girelli R, Mambrini A, Frigerio I, Boz G, Salvia R, et al. Combined modality treatment for patients with locally advanced pancreatic adenocarcinoma. Br J Surg. 2012;99:1083–8.
18. Tempero MA, Malafa MP, Behrman SW, Benson AB, Casper ES, Chiorean EG, et al. Pancreatic adenocarcinoma, version 2.2014: featured updates to the NCCN guidelines. J Natl Compr Canc Netw. 2014;12:1083–93.
19. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228–47.
20. Tol JAMG, Gouma DJ, Bassi C, Dervenis C, Montorsi M, Adham M, et al. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: A consensus statement by the International Study Group on Pancreatic Surgery (ISGPS). Surg (United States). 2014;156:591–600.
21. Tol JAMG, Van Hooft JE, Timmer R, Kubben FJGM, Van Der Harst E, De Hingh IHJT, et al. Metal or plastic stents for preoperative biliary drainage in resectable pancreatic cancer. Gut. 2016;65:1981–7.

22. Frericks BB, Ritz JP, Roggan A, Wolf KJ, Albrecht T. Multipolar radiofrequency ablation of hepatic tumors: Initial experience. Radiology. 2005;237:1056–62.
23. Fegrachi S, Molenaar IQ, Klaessens JH, Besselink MG, Offerhaus JA, Van Hillegersberg R. Radiofrequency ablation of the pancreas with and without intraluminal duodenal cooling in a porcine model. J Surg Res [Internet]. Elsevier Ltd; 2013;184:867–72. Available from: http://dx.doi.org/10.1016/j.jss.2013.04.068
24. Fegrachi S, Molenaar IQ, Klaessens JH, Besselink MG, Offerhaus JA, Van Hillegersberg R. Radiofrequency ablation of the pancreas: Two-week follow-up in a porcine model. Eur J Surg Oncol [Internet]. Elsevier Ltd; 2014;40:1000–7. Available from: http://dx.doi.org/10.1016/j.ejso.2013.11.001
25. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European organization for research and treatment of cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85:365–76.
26. Fitzsimmons D, Johnson CD, George S, Payne S, Sandberg AA, Bassi C, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. Eur J Cancer. 1999;35:939–41.
27. Jun GT, Ward J, Clarkson PJ. Systems modelling approaches to the design of safe healthcare delivery: Ease of use and usefulness perceived by healthcare workers. Ergonomics. 2010;53:829–47.
28. Bonnetain F, Bonsing B, Conroy T, Dousseau A, Glimelius B, Haustermans K, et al. Guidelines for time-to-event end-point definitions in trials for pancreatic cancer. Results of the DATECAN initiative (Definition for the Assessment of Time-to-event End-points in CANcer trials). Eur. J. Cancer. 2014. p. 2983–93.
29. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, et al. Postpancreatectomy hemorrhage (PPH)-An International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery. 2007;142:20–5.
30. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, et al. Delayed gastric emptying (DGE) after pancreatic surgery: A suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2007;142:761–8.
31. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surg (United States) [Internet]. Elsevier Inc.; 2017;161:584–91. Available from: http://dx.doi.org/10.1016/j.surg.2016.11.014
32. Koch M, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L, et al. Bile leakage after hepatobiliary and pancreatic surgery: A definition and grading of severity by the International Study Group of Liver Surgery. Surgery. 2011;149:680–8.
33. Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ. 2013;346.
34. Poon RT, Ng KK, Lam CM, Ai V, Yuen J, Fan ST, et al. Learning Curve for Radiofrequency Ablation of Liver Tumors. Ann Surg. 2004;239:441–9.
35. De Wilde RF, Besselink MGH, Van Der Tweel I, De Hingh IHJT, Van Eijck CHJ, Dejong CHC, et al. Impact of nationwide centralization of pancreaticoduodenectomy on hospital mortality. Br J Surg. 2012;99:404–10.
36. Poplin E, Feng Y, Berlin J, Rothenberg ML, Hochster H, Mitchell E, et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: A trial of the Eastern Cooperative Oncology Group. J Clin Oncol. 2009;27:3778–85.
37. Little RJA, Wang Y. Pattern-Mixture Models for Multivariate Incomplete Data with Covariates. Biometrics. 1996;
38. Hackert T, Sachsenmaier M, Hinz U, Schneider L, Michalski CW, Springfeld C, et al. Locally advanced pancreatic cancer: Neoadjuvant therapy with folfirinox results in resectability in 60% of the patients. Ann Surg. 2016;264:457–61.
39. Rangelova E, Wefer A, Persson S, Valente R, Tanaka K, Orsini N, et al. Surgery Improves Survival After Neoadjuvant Therapy for Borderline and Locally Advanced Pancreatic Cancer. Ann Surg [Internet]. 2019;1. Available from: http://insights.ovid.com/crossref?an=00000658-900000000-95145
40. Giardino A, Girelli R, Frigerio I, Regi P, Cantore M, Alessandra A, et al. Triple approach strategy for patients with locally advanced pancreatic carcinoma. Hpb. 2013;15:623–7.
41. Marthey L, Sa-Cunha A, Blanc JF, Gauthier M, Cueff A, Francois E, et al. FOLFIRINOX for Locally Advanced Pancreatic Adenocarcinoma: Results of an AGEO Multicenter Prospective Observational Cohort. Ann Surg Oncol. 2015;22:295–301.

42. Suker M, Koerkamp BG, Coene PP, van der Harst E, Bonsing BA, Vahrmeijer AL, et al. Yield of staging laparoscopy before treatment of locally advanced pancreatic cancer to detect occult metastases. Eur J Surg Oncol. 2019;45:1906–19.
43. Rombouts SJ, Walma MS, Vogel JA, van Rijssen LB, Wilmink JW, Mohammad NH, et al. Systematic Review of Resection Rates and Clinical Outcomes After FOLFIRINOX-Based Treatment in Patients with Locally Advanced Pancreatic Cancer. Ann Surg Oncol. 2016;23:4352–60.
44. Gemenetzis G, Groot VP, Blair AB, Laheru DA, Zheng L, Narang AK, et al. Survival in Locally Advanced Pancreatic Cancer After Neoadjuvant Therapy and Surgical Resection. Ann Surg [Internet]. 2019;epublished:doi.10.1097/SLA.0000000000002753. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29596120%0Ahttp://insights.ovid.com/crossref?an=00000658-900000000-95664
45. Maggino L, Malleo G, Marchegiani G, Viviani E, Nessi C, Ciprani D, et al. Outcomes of Primary Chemotherapy for Borderline Resectable and Locally Advanced Pancreatic Ductal Adenocarcinoma. JAMA Surg. 2019;154:932–42.
46. Walma MS, Brada LJ, Patuleia SIS, Blomjous JG, Bollen TL, Bosscha K, et al. Treatment strategies and clinical outcomes in consecutive patients with locally advanced pancreatic cancer: A multicenter prospective cohort. Eur J Surg Oncol [Internet]. 2021;47:699–707. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0748798320310337
47. Strijker M, Mackay TM, Bonsing BA, Bruno MJ, van Eijck CHJ, de Hingh IHJT, et al. Establishing and Coordinating a Nationwide Multidisciplinary Study Group: Lessons Learned by the Dutch Pancreatic Cancer Group. Ann Surg. 2020;271:e102–4.

SUPPLEMENTARY MATERIAL

Additional file 1

Eligibility criteria RFA

An ablation can be performed, when the edge of the estimated ablation zone has a safety distance of at least 5 mm to the vital structures (portal vein, superior mesenteric vein, superior mesenteric artery, common hepatic artery, celiac trunk, caval vein, duodenum). The size of the ablation zone is dependent on the electrode and ellipse shaped with a diameter of:

- T9 electrode – 6-8mm
- T15 electrode – 8-10mm
- T20-T40 electrodes – 20mm

Patients with a stenosis of both the portal vein/ superior mesenteric vein and the hepatic artery of > 50% are exluded based on the study teams experience of a case with acute thrombosis of the portal vein and liver failure as a consequence of a compromised hepatic artery.

The expert panel will assess whether patients meet these criteria based on biphasic CT-abdomen after induction chemotherapy. These criteria are based on the principle that the intention of the RFA of pancreatic tumors is essentially a form of tumor debulking rather than total tumor ablation. Besides, recent analysis of previous performed studies did not show a correlation between the size of the necrotic area and the prognosis of the patient.

Additional file 2

Chemotherapy administration

FOLFIRINOX consists of oxaliplatin at a dose of 85 mg/m2, given as a 2-hour intravenous infusion, immediately followed by leucovorin at a dose of 400 mg/m2, given as a 2-hour intravenous infusion, with the addition, after 30 minutes, of irinotecan at a dose of 180 mg/m2, given as a 90-minute intravenous infusion. This treatment will immediately be followed by fluorouracil at a dose of 400 mg/m2, administered by intravenous bolus, followed by a continuous infusion of 2400 mg/m2 over a 46-hour period every two weeks. In total, patients will receive 8 cycles of FOLFIRINOX after randomization.

The regimen of nab-paclitaxel/gemcitabine consists of a 30-to-40-minute intravenous infusion of nab-paclitaxel at a dose of 125 mg/m2, followed by a 30-minute infusion of gemcitabine at a dose of 1000 mg/m2, on days 1, 8 and 15 every four weeks. After randomization patients will receive four cycles.

The gemcitabine cycle consists of a 30-minute intravenous infusion of gemcitabine at a dose of 1000 mg/m2 on day 1, 8 and 15 followed by one week of rest. Patients will be treated with four cycles after randomization.

All patients receive prophylactic anti-emetics.

Modifications in the FOLFIRINOX regimen in case of deviations in neutrophils, platelets, renal and liver function

	Irinotecan	Oxaliplatin	5FU
Neutrophils			
1st x low neutrophils, febrile neutropenia or < 0.5 more than 7 days	Reduce to 150 mg/m^2	Full dose	Omit bolus
2nd x abovementioned	Maintain 150 mg/m^2	Reduce to 60 mg/m^2	Omit bolus
3rd x abovementioned	Stop treatment		
Platelets			
1st x platelets < 75 *10^9/L	Full dose	Reduce to 60 mg/m^2	Reduce bolus and continuous infusion to 75%
2nd x platelets < 75 *10^9/L	Reduce to 150 mg/m^2	Maintain 60 mg/m^2	Reduce bolus and continuous infusion to 75%
3rd x platelets < 75 *10^9/L	Stop treatment		
Renal function			
Creat clearance ≥30 – <50 ml/min	75%	100%	Reduce bolus and continuous infusion to 75%
Creatinine clearance < 30 ml/min	50%	No oxaliplatin	50%
Liver function			
bilirubine 1.5 – 3 x ULN, transaminasen> 5 x ULN	50%	100%	100%
Bilirubine> 3 x ULN	No irinotecan	50%	50%

ULN, upper limit of normal

Stepwise dose reduction for nab-paclitaxel/gemcitabine

Dose level	Nab-paclitaxel (mg/m²)	Gemcitabine (mg/m²)
Full dose	125	1000
1st step dose reduction	100	800
2nd step dose reduction	75	600
When further dose reduction is necessary	Stop treatment	Stop treatment

Dose reductions for nab-paclitaxel/gemcitabine in case of neutropenia or thrombocytopenia.

Day of each cycle	Nab-paclitaxel	Gemcitabine
Day 1		
ANC < 1.5x109 / L OR platelets < 100x109/L	Delay by 1 week intervals until recovery	
Day 8		
500 ≤ ANC < 1000 OR 50.000 ≤ platelets < 75.000	Reduce dose with 1 step	
ANC < 500 OR platelets < 50.000	Hold dose	
Day 15: If day 8: full dose was given		
500 ≤ ANC < 1000 OR 50.000 ≤ platelets < 75.000	Add WBC growth factors to treatment OR decrease dose with 1 step	
ANC < 500 OR platelets < 50,000	Hold dose	Hold dose
Day 15: If day 8: dose reduction		
ANC ≥ 1000 AND platelets ≥ 75,000	Return to dose given at day 1 + WBC growth factors OR same dose as day 8	
500 ≤ ANC < 1000 OR 50.000 ≤ platelets < 75.000	Same dose as day 8 + WBC growth factors OR reduce dose with 1 step compared to day 8	
ANC < 500 or platelets < 50,000	Hold dose	
Day 15: if day 8: dose was hold		
ANC ≥ 1000 and platelets ≥ 75,000	Return to dose given at day 1 + WBC growth factors OR reduce with 1 step compared to day 1	
500 ≤ ANC < 1000 OR 50.000 ≤ platelets < 75.000	Reduce dose with 1 step + WBC growth factors OR Reduce dose with two steps compared to day 1	
ANC < 500 or platelets < 50,000	Hold dose	

ANC, absolute neutrophil count

Dose reductions for nab-paclitaxel/gemcitabine in case of other forms of toxicities

Complication	Nab-paclitaxel	Gemcitabine
Grade 3 or 4 peripheral neuropathy	Hold dose until recovery to at least ≤ grade 1; resume dose reduced with one step.	Treat with the same dose as before
Grade 2 or 3 cutaneous toxicity	Reduce dose with one step; stop treatment when toxicity persists	
Gastro-intestinal toxicity: grade 3 mucositis or diarrhea	Hold dose until recovery to ≤ grade 1; resume dose reduced with one step.	

Dose modifications of gemcitabine

Absolute Neutrophil Count (10^9/L)		Platelets (10^9/L)	Gemcitabine dose (%)
> 1.5	AND	> 75	100
3 1.0 - < 1.5	AND	> 50 - <75	75
< 1.0	OR	< 50	Postponed

Additional file 3

Protocol amendments and approval by METC

Date submitted	Date of approval	New documents	Summary
06-10-2014	-	Protocol v1	Never used, changed to v2 before approval
19-12-2014	24-12-2014	Protocol v2 PIF/IC v2	Clarification patient information
09-03-2015	20-03-2015	Protocol v3	Change protocol writing committee; Investigators; Add immunomodulation as endpoint; Change in- exclusion criteria; criteria for chemotherapy changed; QoI in appendix
13-04-2015	-	Protocol v4	Investigators UMCU, Radboud, RdGG; Change of in- and exclusion criteria; change aim to ablate >50% tumor **into** strive to create widest possible ablation. not used changed to v6 before approval
20-04-2015	-	Protocol v5	FU from start of study treatment instead of randomization. Add stenosis of both portal vein/SMV and hepatic artery as exclusion to appendix 2 Protocol not used changed to v6 before approval
05-06-2015	18-06-2015	Protocol v6	Added study endpoint: time from randomization to start treatment.
31-08-2015	11-11-2015	Protocol v7	Change study coordinator/investigators; criteria for registration; added side study Expect; changed exclusion criteria (portal vein thrombus, second malignancy); FU when patients go to non-PELICAN center for chemotherapy. Added Expect, specify that chemotherapy needs to be given in PELICAN center. Consent to come to outpatient clinics at FU moments.
21-12-2015	12-01-2016	Protocol v8	Added nab-paclitaxel with change of sample size. Added UMCU to Expect side study. Specified when lymph nodes are considered as metastastic. Adjusted flow duodenal cooling at RFA procedure.
18-04-2016	17-06-2016	Protocol 9	Clarification difference between locoregional lymph node metastases vs distance lymph node metastases. Description Celon ProSurge micro Applicators. Clarification criteria for nab-paclitaxel and gemcitabine.
17-01-2018	26-03-2018	Protocol 10	Adjusting title due tuo international centers. Further clarification of dose reductions due to toxicity of FOLFIRINOX.

Additional file 4

SPIRIT checklist

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	
Administrive information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Yes, see title
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Yes, see abstract
	2b	All items from the World Health Organization Trial Registration Data Set	Yes, see trialregister.nl or clinicaltrials.gov
Protocol version	3	Date and version identifier	Yes, 10.2 (6 march 2018) see manuscript 'trial status'
Funding	4	Sources and types of financial, material, and other support	Yes, see Funding, in declaration section
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Yes, see title page p1 and authors contributions, in declaration section
	5b	Name and contact information for the trial sponsor	Yes, see ethics approval in declaration section
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	There was no such role, See funding, in declaration Section
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Yes, every center had a local PI responsible for local procedures and safety monitoring. There was an independent data monitor. See quality and safety section
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Yes, see background
	6b	Explanation for choice of comparators	Intervention vs. standard of Care

Section/item	ItemNo	Description	
Objectives	7	Specific objectives or hypotheses	Yes, see introduction
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Yes, see introduction
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	See registration and Randomization
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Yes, see Eligibility in methods Section
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Yes, see intervention and Control in methods section
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Yes, see intervention and Additional file 2.
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Mainly through telephone Contact between study Coordinator and physicians and patients
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Yes, see censoring reasons and eligibility criteria
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Yes, see study endpoints and definitions
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Yes, see SPIRIT figure. Figure 2

Section/item	ItemNo	Description	
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Yes, see sample size in methods section
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Yes, mainly through intensive follow-up by study coordinator
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Yes, computer generated, Online module by study Coordinator or IKNL
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Yes, online module
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Allocation sequence is Generated by an independent person not involved in Assigning interventions or Enrolling patients
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA, no blinding
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA, no blinding
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Yes, data management grant. Data collection is done by an Independent research agency: IKNL clinical research dpt. Predefined case record forms.

Section/item	ItemNo	Description	
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Case record forms will be used, also for those deviating from intervention.
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Yes, see protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Yes, see protocol and Manuscript: Statistical Analysis
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	see Statistical Analysis
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Yes, see protocol. Intention to treat ánd per protocol analyses
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Yes, data monitoring By IKNL clinical research Department (data monitoring Grant)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Yes, see manuscript and Protocol
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Yes, see Safety section and Data monitoring safety board
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Yes every 20% DSMB will Audit trial and safety.

Section/item	ItemNo	Description	
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Yes, already approved
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Yes, by e-mail and via Website, NA for manuscript
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Yes, at outpatient clinics, after Identification at MDT. By Research nurse or Trial coordinator.
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Yes, integrated within the Informed consent form
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Yes, see protocol + Patient information
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Yes, see manuscript Declaration section
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Yes, see protocol.
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Yes, insurance, included in Pt information
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Yes, newsletters for trial participants and family will be made. Meetings for trial professionals will be organized.
	31b	Authorship eligibility guidelines and any intended use of professional writers	Yes, see protocol.
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA; No plans are made to Grant public access to the dataset.

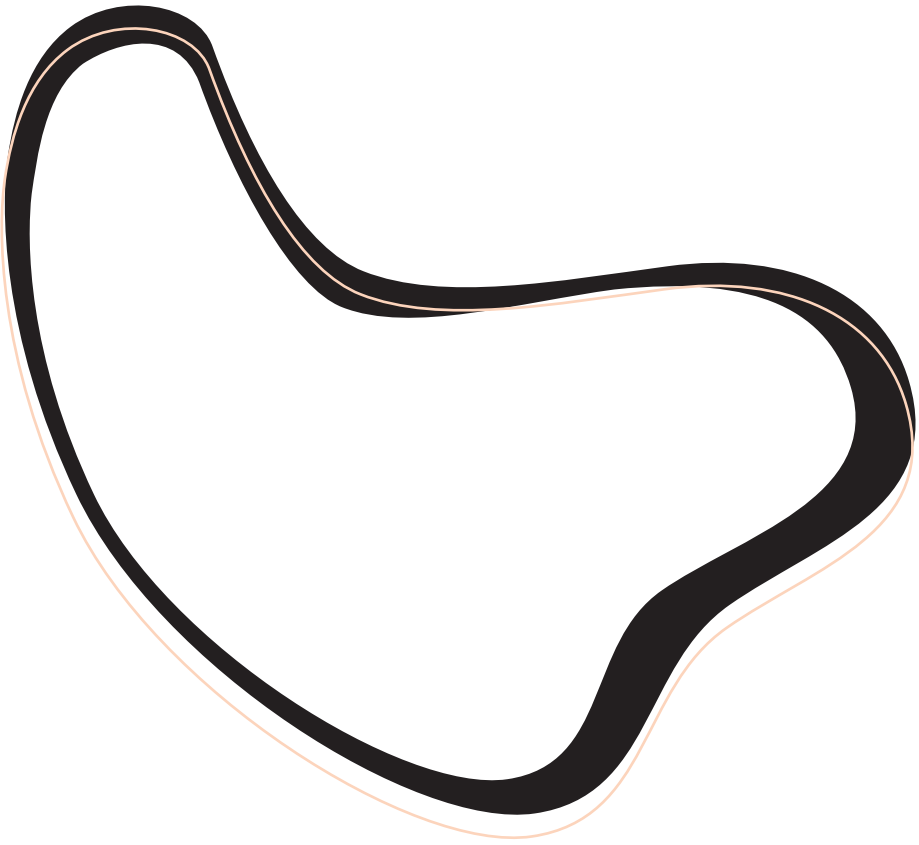
Section/item	ItemNo	Description	
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Yes
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Yes, within biobank.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Summary and discussion

Chapter 11

Summary



This thesis evaluated treatment strategies and clinical outcomes in patients with LAPC in current clinical practice (part I), investigated tools for selecting patients who will undergo a surgical resection or will benefit from chemotherapy (part II), and prepared for the PELICAN trial: a randomized controlled trial investigating the efficacy of radiofrequency ablation in combination with chemotherapy in patients with LAPC (part III).

PART I CURRENT TREATMENT STRATEGIES

Chapter 2. Systematic review on clinical outcomes after FOLFIRINOX-based treatment in LAPC

Since studies often include both patients with LAPC and borderline resectable or metastatic pancreatic cancer, clinical outcomes after FOLFIRINOX-based treatment for LAPC were unclear. This chapter provides a systematic review. Data from 14 studies showed that the resection rate after FOLFIRINOX was 28% and median overall survival ranged between 8.9-25.0 months. The majority of patients was treated with additional radiotherapy. Selection bias occurred in the included studies. Therefore, prospective cohort studies including consecutive patients with LAPC to determine the exact role of FOLFIRINOX in patients with LAPC are needed.

Chapter 3. Overview of treatment strategies in a Dutch multicenter cohort of consecutive patients

This chapter provides an overview of treatment strategies and clinical outcomes within a Dutch multicenter cohort of unselected, consecutive patients with LAPC. In total 77% of all patients started chemotherapy treatment after the diagnosis of LAPC. Most patients (77%) received FOLFIRINOX and had a median overall survival of 14 months. A proportion of 13% underwent a resection after FOLFIRINOX with a median overall survival of 23 months. Patients treated with gemcitabine, with or without nab-paclitaxel, had an overall survival of 9 months. This chapter also showed the lack of treatment paradigms after first-line treatment, with a great variety of multimodal treatment strategies within the cohort. Moreover, the results showed the relevance of reporting data reflecting clinical practice and enable us to inform patients with real world data.

Chapter 4. The treatment and survival of elderly patients with LAPC

The incidence of pancreatic cancer is increasing and life expectancy of the general population is rising. Elderly patients are rarely included in clinical trials and are reported to have worse prognosis. One should question whether this is truly age dependent or due to retaining treatment in the elderly. Hence, in this chapter the association between

increasing age, treatment strategy and survival was investigated. It revealed that patients aged above 75 years, even with a good performance score, were less likely to be treated with chemotherapy. However, with and without adjustment for confounders, elderly patients did not have a worse survival. Although exact reasons for retaining chemotherapy and content of conversations with the medical oncologist were not available in this study, chemotherapy can probably be considered more often in elderly patients with LAPC.

PART II OUTCOME PREDICTION

Chapter 5. Predicting survival and resection after FOLFIRINOX treatment in LAPC

Part I of this thesis showed that selected patients with a diagnosis of LAPC, undergo a resection after FOLFIRINOX and overall survival widely ranges between patients. The aim of chapter 5 was to develop two nomograms to predict at baseline, those patients with favorable outcomes. Overall survival was difficult to predict at baseline (c-index 0.61), but positively influenced by older age, female sex, less comorbidity and a CA19.9 ≤274. A surgical resection was predicted by performance score and vascular involvement at baseline (c-index 0.79), with the best patients having a likelihood for resection after chemotherapy of 35%. The developed nomograms are useful in the discussion between the patient and their clinicians whether or not to start treatment with FOLFIRINOX.

Chapter 6. Intra-operative ultrasound to assess resectability after FOLFIRINOX in LAPC

Selecting patients with LAPC for a possible resection after FOLFIRINOX is challenging because CT cannot reliably discriminate viable tumor from post-chemotherapy tumor fibrosis. Therefore, the true vascular involvement is difficult to evaluate. In this chapter the value of intra-operative ultrasound was investigated and findings were compared to preoperative CT-scans. Tumor stage was evaluated different when compared to preoperative CT-scan in 32% of cases and tumor diameters were significantly smaller upon intra-operative ultrasound. Intra-operative ultrasound facilitates the decision to proceed with an exploration, but it does not contribute to the selection in the preoperative setting. Future studies should also focus on improving preoperative selection tools, like magnetic resonance imaging or endoscopic ultrasound.

Chapter 7. Predicting occult metastases in patients with presumed resectable pancreatic cancer

Approximately 10-20% of patients with presumed (borderline) resectable pancreatic cancer turn out unresectable during surgical exploration due to distant metastases. This

chapter describes a preoperative prediction model for occult metastases during exploratory laparotomy developed in the Dutch Pancreatic Cancer Audit database. In this cohort 10% had occult metastases and these were associated with higher age, lower body mass index, the need for nutritional support in advance of surgery, a larger tumor diameter, a solid tumor composition (versus cystic) and indeterminate lesions on preoperative imaging. External validation showed that the associated variables where not sufficient to build a robust predictive model. Future studies should look into biological markers added to the current parameters as potential predictors for occult metastases.

PART III LOCAL ABLATIVE THERAPIES

Chapter 8. Eligibility for radiofrequency ablation and irreversible electroporation in LAPC

Local ablative therapies are increasingly used in patients with LAPC. Two comparable strategies, with a different mechanism of action, are investigated in Chapter 8. A literature review was performed to summarize eligibility criteria for radiofrequency ablation (RFA) and irreversible electroporation (IRE). These criteria were retrospectively applied to a cohort of patients to get insight in the extent of overlap or exclusiveness in eligibility for these two strategies. It showed that 91% of patients with LAPC was eligible for at least one of both therapies. RFA appeared to be more suitable for larger tumors since the need to leave a safety rim of non-ablated tissue to vital structures. Tumors that grow cuff-like along vascular structures seem to be more eligible for IRE. A significant proportion of patients was eligible for only one of both strategies (45%), so that it is important to proceed studies on the safety and efficacy of IRE as well as RFA.

Chapter 9. Safety of radiofrequency ablation in LAPC

In preparation for a randomized controlled trial, the safety of RFA was investigated in chapter 9 of this thesis. Patients with LAPC, confirmed during a surgical exploration, were treated with RFA in the same surgical session. RFA was performed with direct intra-operative ultrasound guidance and a predefined distance was kept to vital structures. Results showed that RFA should be considered as a major procedure. A high frequency (46%) of delayed gastric emptying (DGE) occurred, mostly after gastrojejunostomy. Major morbidity other than DGE was 29% and was within the predefined acceptable amount. No pancreatic fistulas, pancreatitis or duodenal perforations occurred. Within this chapter the safety of RFA pancreas in patients with LAPC was established, when taking strict safety measures with predefined distances of the RFA probe to vital surrounding structures.

Chapter 10. PELICAN trial: a randomized controlled trial on the efficacy of radiofrequency ablation

Based on chapter 9, an international multicenter randomized controlled trial was designed with a national multidisciplinary collaboration: the Dutch Pancreatic Cancer Group. Chapter 10 presents the study protocol of the PELICAN trial. Patients with LAPC, who have stable disease or an objective response without the possibility for a resection, after 2 months of chemotherapy are eligible for inclusion. Eligible patients are randomized to intra-operative RFA followed by continuation of chemotherapy versus chemotherapy without RFA. The primary outcome of the PELICAN trial is overall survival. Patient recruitment is estimated to be completed in December 2021.

SUMMARY OF RESEARCH QUESTIONS AND MAIN FINDINGS

Chapter	Research question and main finding
2	**What are the clinical outcomes in published studies on FOLFIRINOX-based therapy in patients with LAPC?** The resection rate after FOLFIRINOX was 28% and median overall survival ranged between 8.9 and 25.0 months. The majority of patients was treated with additional radiotherapy.
3	**What are the current treatment strategies and outcomes in a nationwide cohort of consecutive patients with LAPC?** 77% of all patients started chemotherapy, mostly FOLFIRINOX (77%) with a median overall survival of 14 months. 13% underwent a resection after FOLFIRINOX (median overall survival: 23 months). Patients treated with gemcitabine, with or without nab-paclitaxel, had an overall survival of 9 months. There was a great variety of multimodal treatment strategies within the cohort.
4	**Is the age of patients with LAPC associated with treatment strategy and overall survival?** Patients aged above 75 years, even with a good performance score, were less likely to be treated with chemotherapy. However, with and without adjustment for confounders, elderly patients did not have a worse survival.
5	**What are predictors for overall survival and resection for patients with LAPC at the start of treatment with FOLFIRINOX?** Overall survival was positively influenced by older age, female sex, less comorbidity and a CA19.9 ≤274 (c-index 0.61). A surgical resection was predicted by performance score and vascular involvement at baseline (c-index 0.79), with the best patients having a likelihood for resection after chemotherapy of 35%.
6	**Does intra-operative ultrasound contribute in selecting patients with LAPC for a surgical resection following FOLFIRINOX chemotherapy?** Tumor stage was evaluated different when compared to preoperative CT-scan in 32% of cases. Intra-operative ultrasound facilitates the decision to proceed with an exploration, but it does not contribute to the selection in the preoperative setting.

7	**What are preoperative clinical predictors of occult metastases during explorative laparotomy in patients with presumed (borderline) resectable pancreatic cancer?** Occult metastases were associated with higher age, lower body mass index, the need for nutritional support in advance of surgery, a larger tumor diameter, a solid tumor composition (versus cystic) and indeterminate lesions on preoperative imaging.
8	**What are the eligibility criteria for IRE and RFA and what is the extent of overlap or exclusiveness in eligibility for RFA and IRE in patients with LAPC?** 91% of patients with LAPC is eligible for at least one of both therapies and 45% is eligible for only one of both strategies. RFA appeared to be more suitable for larger tumors. Tumors that grow cuff-like along vascular structures seem to be more eligible for IRE.
9	**Is RFA a safe treatment strategy for patients with LAPC?** Although RFA is a major procedure, safety of RFA pancreas was established with a morbidity of 29% (other than delayed gastric emptying). No pancreatic fistulas, pancreatitis or duodenal perforations occurred.
10	**Does the combination of chemotherapy and RFA improves overall survival in patients with LAPC when compared to chemotherapy alone?** This research question cannot yet be answered since PELICAN trial inclusion is ongoing.

Chapter 12

General discussion and future perspectives

Treatment strategies in patients with LAPC have developed over the years, aiming to improve overall survival. Initial reports often showed encouraging results with sometimes an overall survival comparable to patients with upfront resectable disease.[1,2,3] Nevertheless, clinical practitioners remain skeptical on upcoming therapies since randomized studies are currently lacking and cohorts consist of highly selected patients which do not reflect current clinical practice. Research presented in this thesis provides a reference standard for current clinical practice (part I), gives insight in patient selection to guide treatment decisions (part II), and forms the basis of a multicenter randomized controlled trial, the PELICAN trial, investigating a local treatment strategy in patients with LAPC (part III). The relevance of the results within the context of existing knowledge, and future perspectives are further discussed here.

Current clinical practice

Chemotherapy

The landmark randomized controlled trial by Conroy *et al.* showed a survival benefit of 4.3 months after treatment with FOLFIRINOX when compared to gemcitabine monotherapy in patients with metastasized pancreatic cancer.[4] As summarized in **Chapter 2**, encouraging results were reported for patients with LAPC as well, with a survival up to 25 months. Initially, some medical oncologists were reluctant for its use, due to concerns on the high level of toxicity. Grade 3-4 neutropenia was described in 46% of patients and 13-15% developed grade 3-4 vomiting or diarrhea.[4] Moreover, inclusion criteria of oncological trials do not seem to reflect the patient population that consult physicians on their outpatient clinic.[5,6] **Chapter 3** of this thesis provides important information for these clinical practitioners, since it represents a real time cohort with consecutive patients with LAPC from all over the Netherlands. It learned us that 21% of patients do not start any oncological treatment after diagnosis. In about half of the time, this is a deliberate decision of a patient who is eligible for treatment, but considers their quality of life better without. This thesis also showed that the majority of patients (77%) treated with chemotherapy, is currently receiving FOLFIRINOX, and toxicity was less than expected. A broadening of eligibility criteria is seen and nowadays more elderly patients are treated with sometimes a modified FOLFIRINOX regimen omitting or reducing the 5-FU bolus (**Chapter 4**). With the aging of the general population and the decrease of toxicity it becomes more important to discuss this therapy with elderly patients, so that they can make a deliberate choice whether to start chemotherapy. Although there still might be some referral bias in the study described in **Chapter 3**, these data better reflect daily clinical practice. Results are in line with a recently published study from Maggino *et al.* from Verona[7], while until now survival data up to 25 months were reported. This thesis and the study of Maggino *et al.* both reported a more realistic overall survival of 13 to 14 months for all patients with LAPC. In addition,

a similar resection rate of 9% in all patients that presented with LAPC, and 13% in patients that finished chemotherapy was reported.[7] Especially in the palliative setting, it is of vital importance to make a balanced decision, together with the patient, if a possible toxic regimen is worth starting. To guide these decisions, the real world information from this thesis on survival, resection rates and toxicity are helpful.

Although overall survival after FOLFIRINOX is less beneficial than suggested in studies from selected cohorts, the survival range is wide. Those patients with a survival of more than 20 months do exist, and in the ideal situation we would like to identify those patients in advance of starting therapy. **Chapter 5** identified female sex as a possible predictor for a better overall survival after treatment with FOLFIRINOX, among a low serum CA19.9, older age and a low comorbidity score. Especially CA19.9 has often been described as a predictor for overall survival in patients with pancreatic cancer.[8,9] High serum CA19.9 levels suggest micro-metastatic disease or a high disease load.[10] Other studies also showed response to chemotherapy and sometimes a resection as positive prognostic factors.[2,11] However, the intention of this chapter was to predict outcomes before the start of treatment, since only than nomograms can be used in clinical practice. It seemed hard to predict survival (c-index 0.61), nevertheless **Chapter 5** can be a start for further modelling.

For the relatively novel combination treatment with nab-paclitaxel and gemcitabine, data from this thesis are immature. Within the Netherlands, nab-paclitaxel/gemcitabine was registered as a treatment for pancreatic cancer from July 2015. Thereafter it was implemented within standard of care, mostly for WHO 1-2 patients, explaining the unfavorable baseline characteristics of patients treated with nab-paclitaxel/gemcitabine within **Chapter 3**. In contrast to our results, a recent phase 2 study reported an overall survival of 18.8 months and a 33.6% response rate in 107 patients with LAPC treated with this regimen.[12] A phase II trial from Japan started in July 2016 and randomizes patients with LAPC between modified FOLFIRINOX and nab-paclitaxel/gemcitabine with 1-year overall survival as primary endpoint.[13] Another trial from France is investigating the conversion rate to resectability in patients treated with nab-paclitaxel/gemcitabine versus FOLFIRINOX.[14] While awaiting the results of these studies, we cannot yet draw conclusions on the superiority of one of these 2 regimens.

Concerning gemcitabine monotherapy, it might be that this regimen will slowly disappear. Nowadays, more medical oncologists choose nab-paclitaxel/gemcitabine as alternative for gemcitabine monotherapy, despite limited evidence.[15] We reported only 13% of patients treated with this regimen (**Chapter 3)**. Moreover, in patients with metastasized disease, it never showed a survival benefit, but an improvement of quality of life has been reported.[16]

Resection of LAPC after chemotherapy

In **Chapter 3** it is described that 13% of patients with LAPC treated with FOLFIRINOX will undergo a resection. This is less promising than described within several cohort studies, with an average of 28% of resections after FOLFIRINOX in patients with LAPC (**Chapter 2**). A study of Hackert *et al.* from Heidelberg reported resectability in 60% of patients with LAPC.[17] However, only patients who underwent a surgical exploration after FOLFIRINOX were included in the denominator, representing a selection of patients that started with FOLFIRINOX. Although some centers advocate an explorative laparotomy as standard procedure for all patients without progression of disease, most hospitals do not proceed to a surgical exploration regularly. In the study in **Chapter 3,** the decision to proceed to a surgical exploration was made within a nationwide experienced expert panel, based on pre- and post-chemotherapy imaging. This might have underestimated the eligibility for a resection since studies described the unability of CT-imaging to distinguish between viable tumor tissue and fibrosis after chemotherapy.[18] **Chapter 5** describes that intra-operative ultrasound showed different vascular involvement when compared to preoperative CT imaging. During surgery, in some cases it facilitated decision making to proceed with a resection. However the challenge of preoperative patient selection remains. With this reason some other studies, with higher resection rates, perform a surgical exploration in all patients without progression of disease.[2]

Despite the increase of publications on conversion to a resection, the true effect of a resection in terms of survival benefit in addition to the effect of FOLFIRINOX has not yet been established. This impedes the decision how far we should go for a surgical resection and also causes discussion on the exact definition of unresectable pancreatic cancer. The latter becomes obvious when looking at different guidelines and publications using different definitions for LAPC.[2,10,19-21] Where most centers do not perform arterial resections due to the potential high morbidity and mortality, some other centers do, or even perform resection of tumor metastases.[22] Others argue that also biological factors, such as CA19-9, should be taken into account when defining a patient as unresectable.[10] In conclusion, many questions remain to be answered on the exact role of a resection after FOLFIRINOX and the associated definition of LAPC.

One of the main issues when performing an explorative laparotomy with the intention for resection are occult metastases. In patients with LAPC, 19% had occult metastases at diagnosis.[23] For these patients, a resection after chemotherapy does not seem beneficial. Within the current era of increasing resection rates after FOLFIRINOX in this patient population, it might be argued that a staging laparoscopy must be performed for all patients at diagnosis. The aim of **Chapter 7** was to develop a tool to identify

patients at high risk for occult metastases. Unfortunately the developed model fell short at external validation. It is uncertain which factors contributed to this disappointing external validity and it is worthwhile to further look into this within other cohorts.

Radiotherapy

This thesis shows that radiotherapy is not embedded in the standard treatment regimen for patients with locally advanced pancreatic cancer in the Netherlands. This is different from other centers worldwide. For example, the National Comprehensive Cancer Network (NCCN) guidelines offer chemoradiation or stereotactic body radiation as option for first-line therapy.[20] This disparity in treatment strategies is caused by conflicting results from available studies. The LAP07 randomized patients with LAPC for gemcitabine versus gemcitabine with erlotinib, whereafter a second randomization for continuing chemotherapy versus chemoradiotherapy was performed.[24] No benefit of chemoradiotherapy was seen when compared to continuation of chemotherapy alone, but the study was underpowered. With SBRT a more precise application of high-dose radiation can be delivered to a limited target volume, potentially limiting the radiation dose to adjacent healthy tissue. A study including over 14,000 patients did show a significantly better survival for patients treated with chemotherapy with stereotactic body radiation (SBRT) versus chemotherapy alone.[25] However, this was a retrospective study, and confounding by indication may be present. Moreover, a Dutch study reported a median OS of 17 months with 5% gastro-intestinal bleeding leading to death within three months after SBRT.[26] Results are not yet convincing enough to reach consensus and embed SBRT as standard of care for patients with LAPC in the Netherlands.

Future perspectives

An important gap in current knowledge on LAPC is reliable data on quality of life. Quality of life is currently being measured within the Dutch Pancreatic Cancer Project (PACAP)[27] and we are awaiting results for patients with LAPC treated with the different treatment regimens. Especially in this palliative setting, it is of vital importance to make a balanced decision whether to start treatment, including data on quality of life. This thesis learned us, that no treatment paradigm exists after first line chemotherapy. This emphasizes the importance to further look into the efficacy of second line therapies, so that a standardized treatment can be defined. In addition, new treatment strategies keep being developed and research concerning for example immunotherapy is ongoing.[28] Since the prediction of survival based upon patient, laboratory and radiologic information remains difficult, further steps should be made towards individualized therapy. It seems that translational research can play a role, such as circulating tumor-DNA, circulating tumor-cells, other biomarkers and tumor organoids.[29] In the end, it

seems that tumor biology is an important factor determining tumor behavior and patient survival in pancreatic cancer. Future research should focus on these kind of translational models combined with clinical predictors.

Lastly, added survival benefit from resection after FOLFIRINOX compared to the survival of FOLFIRINOX alone should be elucidated. Future studies should match resected and non-resected patients on vascular involvement, RECIST response and CA19.9. Whereafter the exact survival benefit of an additional resection in LAPC should be determined in prospective studies.

Local ablative therapies

The Verona group developed a procedure wherein one or more RFA probes are placed with ultrasound guidance in the center of a tumor during a laparotomy. With an ablation not exceeding into healthy pancreatic tissue or nearby structures, together with a maximum probe temperature of 90 degrees, overall morbidity was acceptable (26%).[30] Another local ablative therapy, IRE, was mainly developed within the study group of Martin *et al.* (open procedure) and Narayanan *et al.* (imaging guided percutaneous procedure).[31,32] This method requires multiple electrodes to be placed surrounding the tumor borders with ultrasound guidance. For both strategies, it has been shown that a systemic immune response is induced, possibly due to a transitional zone of apoptosis-undergoing tumor tissue exposing tumor-specific antigens.[33,34] In preparation of the design for an international randomized controlled superiority trial a review was performed.[35] This review showed both IRE and RFA as potential promising therapies. In the study in **Chapter 8,** we investigated eligibility of patients for both therapies, since not all tumors are technically fit for ablation. It taught us that RFA is more applicable in bulky tumors, but less in tumors growing in a manchet-like manner around the central vessels. An important reason to proceed with research on RFA was that it is already broadly implemented in standard of care for other tumor types.[36] This makes RFA more readily available with shorter learning curves and a greater availability at lower costs. Moreover, more recent studies on IRE performed within the Netherlands, showed a relatively high morbidity, while with radiofrequency ablation 24% of complications were described.[35,37,38] After frequent visits and intensive contact with Verona, two animal studies were performed and the safety was established within a phase 2 trial **(Chapter 9)**. Eligibility criteria were further defined, especially the distance to be held from vital structures with different probes, aiming for a safety rim. Together with the Dutch Pancreatic Cancer Group (DPCG), the PELICAN trial was designed **(Chapter 10).** This is currently the only ongoing registered study that compares an ablative therapy as multimodal treatment strategy directly with chemotherapy in a randomized setting in patients with LAPC.

Future perspectives

The results of the PELICAN trial will be of great importance to value the relevance of RFA in patients with LAPC. The multidisciplinary character of the DPCG with great experience with multicenter trials gives confidence that there will be an answer to this important research question within the following years. If the combination of chemotherapy with RFA shows superiority compared to chemotherapy alone, it is important to also proceed with randomized trials on IRE and other ablative strategies, since not all patients are eligible for RFA **(Chapter 8)**. Moreover, minimal invasive approaches for RFA, i.e. percutaneously and endoscopic, should then be further developed and combination therapy with immunomodulatory drugs might further improve overall survival.[33,34] When the PELICAN trial shows no benefit of RFA, future studies should look into the possible reasons. If local tumor control will not be achieved with RFA, there might still be a role for other local ablative therapies aiming for total tumor ablation. However, when RFA will show no survival benefit, despite local control, the suggestion might rise that other local strategies without systemic effects will not be helpful as well. This suggestion will clearly have to be confirmed by further randomized trials. In summary, the results of the PELICAN trial will be of great importance to guide future research in LAPC.

CONCLUSION

The LAPC registry cohort as described within this thesis enables the Dutch clinical practitioners to inform patients with real world data on survival and resection after FOLFIRINOX among other regimens. Especially in a palliative setting, correct and realistic patient information to support shared decision making is of vital importance. Future research should focus on quality of life and the exploration of biomarkers predicting treatment response, to develop individualized treatment strategies. Moreover, this thesis provides the basis for the PELICAN trial. When finished, the results of this trial can give direction for future research on novel treatment strategies and ideally will further improve overall survival and quality of life for patients with LAPC.

REFERENCES

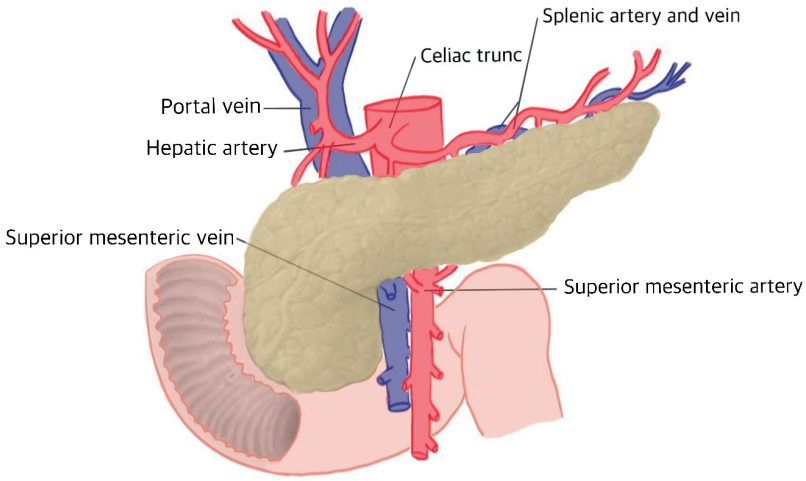
1. Gemenetzis G, Groot VP, Blair AB, et al. Survival in Locally Advanced Pancreatic Cancer After Neoadjuvant Therapy and Surgical Resection. *Ann Surg*. 2019;epublished:doi.10.1097/SLA.0000000000002753. doi:10.1097/SLA.0000000000002753
2. Rangelova E, Wefer A, Persson S, et al. Surgery Improves Survival After Neoadjuvant Therapy for Borderline and Locally Advanced Pancreatic Cancer. *Ann Surg*. Published online 2019:1. doi:10.1097/SLA.0000000000003301
3. Mizrahi JD, Surana R, Valle JW, Shroff RT. Pancreatic cancer. *Lancet*. 2020;395:2008–20. doi:10.1016/S0140-6736(20)30974-0
4. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364(19):1817-1825. doi:10.1056/NEJMoa1011923
5. David JM, Kim S, Placencio-Hickok VR, Torosian A, Hendifar A, Tuli R. Treatment strategies and clinical outcomes of locally advanced pancreatic cancer patients treated at high-volume facilities and academic centers. *Adv Radiat Oncol*. 2019;4(2):302-313. doi:10.1016/j.adro.2018.10.006
6. Amini A, Jones BL, Stumpf P, et al. Patterns of Care for Locally Advanced Pancreatic Adenocarcinoma Using the National Cancer Database. *Pancreas*. 2017;46(7):904-912. doi:10.1097/MPA.0000000000000876
7. Maggino L, Malleo G, Marchegiani G, et al. Outcomes of Primary Chemotherapy for Borderline Resectable and Locally Advanced Pancreatic Ductal Adenocarcinoma. *JAMA Surg*. 2019;154(10):932-942. doi:10.1001/jamasurg.2019.2277
8. Ferrone CR, Finkelstein DM, Thayer SP, Muzikansky A, Castillo CF, Warshaw AL. Perioperative CA19-9 Levels Can Predict Stage and Survival in Patients With Resectable Pancreatic Adenocarcinoma. *J Clin Oncol*. 2006;24(18):2897-2902. doi:10.1200/JCO.2005.05.3934
9. van Veldhuisen E, Vogel JA, Klompmaker S, et al. Added value of CA19-9 response in predicting resectability of locally advanced pancreatic cancer following induction chemotherapy. *HPB*. 2018;20(7):605-611. doi:10.1016/j.hpb.2018.01.001
10. Isaji S, Mizuno S, Windsor JA, et al. International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. *Pancreatology*. Published online 2018. doi:10.1016/j.pan.2017.11.011
11. Barreto SG, Loveday B, Windsor JA, Pandanaboyana S. Detecting tumour response and predicting resectability after neoadjuvant therapy for borderline resectable and locally advanced pancreatic cancer. *ANZ J Surg*. 2019;89(5):481-487.
12. Philip PA, Lacy J, Portales F, et al. Nab-paclitaxel plus gemcitabine in patients with locally advanced pancreatic cancer (LAPACT): a multicentre, open-label phase 2 study. *Lancet Gastroenterol Hepatol*. 2020;5(3):285-294. doi:10.1016/S2468-1253(19)30327-9
13. Mizusawa J, Fukutomi A, Katayama H, et al. Protocol digest of randomized phase II study of modified FOLFIRINOX versus gemcitabine plus nab-paclitaxel combination therapy for locally advanced pancreatic cancer: Japan clinical oncology group study (JCOG1407). *Pancreatology*. 2018;18(7):841-845. doi:10.1016/j.pan.2018.07.007
14. Kunzmann V, Algül H, Goekkurt E, et al. Conversion rate in locally advanced pancreatic cancer (LAPC) after nab-paclitaxel/gemcitabine- or FOLFIRINOX-based induction chemotherapy (NEOLAP): Final results of a multicenter randomised phase II AIO trial. *Ann Oncol*. 2019;30:v253. doi:10.1093/annonc/mdz247
15. van Veldhuisen E, van den Oord C, Brada LJ, et al. Locally Advanced Pancreatic Cancer: Work-Up, Staging, and Local Intervention Strategies. *Cancers (Basel)*. 2019;11(7):976. doi:10.3390/cancers11070976
16. Burris HA, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomized trial. *J Clin Oncol*. 1997;15(6):2403-2413. doi:10.1200/JCO.1997.15.6.2403
17. Hackert T, Sachsenmaier M, Hinz U, et al. Locally advanced pancreatic cancer: Neoadjuvant therapy with folfirinox results in resectability in 60% of the patients. *Ann Surg*. 2016;264(3):457-461. doi:10.1097/SLA.0000000000001850
18. Ferrone CR, Marchegiani G, Hong TS, et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. *Ann Surg*. 2015;261(1):12-17. doi:10.1097/SLA.0000000000000867
19. Dutch Pancreatic Cancer Group. Definitions of resectability pancreatic cancer. Published 2012. Accessed March 13, 2019. http://www.dpcg.nl/richtlijnen-classificaties/dpcg-definities.html

20. Tempero MA, Malafa MP, Al-Hawary M, et al. Pancreatic adenocarcinoma, version 2.2017: Clinical practice guidelines in Oncology. *JNCCN J Natl Compr Cancer Netw*. 2017;15(8):1028-1061. doi:10.6004/jnccn.2017.0131
21. Bockhorn M, Uzunoglu FG, Adham M, et al. Borderline resectable pancreatic cancer: A consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). *Surg (United States)*. Published online 2014. doi:10.1016/j.surg.2014.02.001
22. Del Chiaro M, Rangelova E, Halimi A, et al. Pancreatectomy with arterial resection is superior to palliation in patients with borderline resectable or locally advanced pancreatic cancer. *HPB*. Published online 2019. doi:10.1016/j.hpb.2018.07.017
23. Suker M, Koerkamp BG, Coene PP, et al. Yield of staging laparoscopy before treatment of locally advanced pancreatic cancer to detect occult metastases. *Eur J Surg Oncol*. 2019;45(10):1906-1919. doi:10.1016/j.ejso.2019.06.004
24. Hammel P, Huguet F, Van Laethem JL, et al. Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib the LAP07 randomized clinical trial. *JAMA - J Am Med Assoc*. Published online 2016. doi:10.1001/jama.2016.4324
25. de Geus SWL, Eskander MF, Kasumova GG et al Stereotactic body radiotherapy for unresected pancreatic cancer: A nationwide review. *Cancer*. 2017; Nov 1;123(21):4158-4167. doi: 10.1002/cncr.30856.
26. Suker M, Nuyttens JJ, Eskens FALM, et al. Efficacy and feasibility of stereotactic radiotherapy after folfirinox in patients with locally advanced pancreatic cancer (LAPC-1 trial). *EClinicalMedicine*. Published online 2019. doi:10.1016/j.eclinm.2019.10.013
27. MacKay TM, Smits FJ, Latenstein AEJ, et al. Impact of nationwide enhanced implementation of best practices in pancreatic cancer care (PACAP-1): A multicenter stepped-wedge cluster randomized controlled trial. *Trials*. Published online 2020. doi:10.1186/s13063-020-4180-z
28. Kotteas E, Saif MW, Syrigos K. Immunotherapy for pancreatic cancer. *J Cancer Res Clin Oncol*. 2016;142(8):1795-1805. doi:10.1007/s00432-016-2119-2
29. Boj SF, Hwang C Il, Baker LA, et al. Organoid models of human and mouse ductal pancreatic cancer. *Cell*. Published online 2015. doi:10.1016/j.cell.2014.12.021
30. Girelli R, Frigerio I, Giardino A, et al. Results of 100 pancreatic radiofrequency ablations in the context of a multimodal strategy for stage III ductal adenocarcinoma. *Langenbeck's Arch Surg*. 2013;398(1):63-69. doi:10.1007/s00423-012-1011-z
31. Martin RCG, Kwon D, Chalikonda S, et al. Treatment of 200 locally advanced (Stage III) pancreatic adenocarcinoma patients with irreversible electroporation safety and efficacy. In: *Annals of Surgery*. ; 2015. doi:10.1097/SLA.0000000000001441
32. Narayanan G, Hosein PJ, Beulaygue IC, et al. Percutaneous Image-Guided Irreversible Electroporation for the Treatment of Unresectable, Locally Advanced Pancreatic Adenocarcinoma. *J Vasc Interv Radiol*. Published online 2017. doi:10.1016/j.jvir.2016.10.023
33. Giardino A, Innamorati G, Ugel S, et al. Immunomodulation after radiofrequency ablation of locally advanced pancreatic cancer by monitoring the immune response in 10 patients. *Pancreatology*. 2017;17(6):962-966. doi:10.1016/j.pan.2017.09.008
34. Scheffer HJ, Stam AGM, Geboers B, et al. Irreversible electroporation of locally advanced pancreatic cancer transiently alleviates immune suppression and creates a window for antitumor T cell activation. *Oncoimmunology*. 2019 Aug 28;8(11):1652532. doi: 10.1080/2162402X.2019.1652532. eCollection 2019.
35. Rombouts SJE, Vogel JA, Van Santvoort HC, et al. Systematic review of innovative ablative therapies for the treatment of locally advanced pancreatic cancer. *Br J Surg*. 2015;102(3):182-193. doi:10.1002/bjs.9716
36. Di Martino M, Rompianesi G, Mora-Guzmán I, Martín-Pérez E, Montalti R, Troisi RI. Systematic review and meta-analysis of local ablative therapies for resectable colorectal liver metastases. *Eur J Surg Oncol*. Published online 2020.
37. Vogel JA, Rombouts SJ, de Rooij T, et al. Induction Chemotherapy Followed by Resection or Irreversible Electroporation in Locally Advanced Pancreatic Cancer (IMPALA): A Prospective Cohort Study. *Ann Surg Oncol*. 2017;24(9):2734-2743. doi:10.1245/s10434-017-5900-9
38. Scheffer HJ, Vroomen LGPH, De Jong MC, et al. Ablation of locally advanced pancreatic cancer with percutaneous irreversible electroporation: Results of the phase I/II PANFIRE study. *Radiology*. Published online 2017. doi:10.1148/radiol.2016152835

Appendices

DUTCH SUMMARY | NEDERLANDSE SAMENVATTING

Wereldwijd worden er ruim 495,000 patiënten per jaar gediagnosticeerd met alvleesklierkanker (pancreascarcinoom). De alvleesklier is omgeven door grote en belangrijke bloedvaten (Figuur 1). Deze bloedvaten zijn direct afkomstig van de aorta of poortader en verzorgen de bloedcirculatie van een groot deel van de maag, milt, darmen en lever. Doordat het pancreascarcinoom vaak geen of aspecifieke klachten geeft, is bij veel patiënten de ziekte al gevorderd als de diagnose wordt gesteld. Ongeveer 30 tot 40% van hen heeft nog geen uitzaaiingen, maar wel lokaal gevorderde ziekte (LAPC), waarbij de tumor in of rondom de belangrijke bloedvaten groeit. Deze bloedvaten zijn onmisbaar, daarom is een operatie niet zinvol en is de behandeling veelal palliatief.



Figuur 1. De alvleesklier en omliggende bloedvaten

De standaardbehandeling voor patiënten met een lokaal gevorderd pancreascarcinoom is chemotherapie. De laatste jaren zijn er nieuwe therapieën beschikbaar gekomen. De belangrijkste is FOLFIRINOX-chemotherapie. Deze behandeling werd in eerste instantie onderzocht in patiënten mét uitzaaiingen en blijkt een verbetering van de mediane overleving te geven ten opzichte van gemcitabine chemotherapie (11.1 versus 6.8 maanden). Ook nab-paclitaxel gecombineerd met gemcitabine geeft in patiënten met uitzaaiingen een kleine overlevingswinst (8.7 versus 6.6 maanden). Ondanks dat deze behandelingen niet in een gerandomiseerde studie voor patiënten met een lokaal gevorderd pancreascarcinoom zijn onderzocht, worden ze de laatste jaren wel veelvuldig

toegepast in deze populatie. Het is niet precies bekend welke patiënten hier wel of geen voordeel bij hebben. Sommigen zullen vooral last hebben van bijwerkingen, waar anderen zoveel baat hebben bij chemotherapie dat ze alsnog in aanmerking komen voor een chirurgische verwijdering van de tumor.

Het onderzoek in dit proefschrift focust op de huidige behandelstrategieën en uitkomsten in een grote, representatieve groep patiënten met een lokaal gevorderd pancreascarcinoom in Nederland (deel I). In deel II worden voorspellende factoren onderzocht, met als doel patiënten te selecteren die baat zullen hebben bij chemotherapie. Tot slot wordt de haalbaarheid en veiligheid van een nieuwe, lokale behandeloptie in combinatie met chemotherapie onderzocht, in voorbereiding op een internationale gerandomiseerde studie: de PELICAN-studie (deel III).

Deel I Huidige behandelstrategieën

Hoofdstuk 2. Samenvatting van de literatuur: uitkomsten na FOLFIRINOX-chemotherapie
Om de uitkomsten na deze chemotherapie te onderzoeken bij patiënten met een lokaal gevorderd pancreascarcinoom zijn de resultaten van deze specifieke groep uit 14 studies systematisch samengevat. Dit was nodig omdat studies vaak resultaten van patiënten met een lokaal gevorderd pancreascarcinoom combineren met de uitkomsten van patiënten met uitzaaiingen of borderline operabele ziekte. Op basis van de data wordt in 28% van de gevallen alsnog een operatie verricht na FOLFIRINOX. De overleving varieert tussen de 8.9 en 25 maanden. De patiënten uit de studies zijn waarschijnlijk niet representatief voor de gehele populatie met deze vorm van pancreascarcinoom, maar een selectie patiënten in relatief goede conditie die behandeld kunnen worden met FOLFIRINOX-chemotherapie.

Hoofdstuk 3. Een overzicht van de behandelstrategieën in het LAPC registratie cohort
In dit hoofdstuk worden de uitkomsten van de behandeling van 422 patiënten met een lokaal gevorderd pancreascarcinoom uit 14 verschillende Nederlandse ziekenhuizen weergegeven. Alle patiënten uit deze ziekenhuizen zijn geïncludeerd, zonder een selectie te maken op basis van behandeling of conditie. 77% van alle patiënten start met chemotherapie, daarvan krijgt de meerderheid FOLFIRINOX (77%). De mediane overleving van deze patiënten is 14 maanden. In dit cohort wordt bij 13% van de patiënten, behandeld met FOLFIRINOX, alsnog een operatie verricht na de chemotherapie behandeling. Zij hebben een overleving van 23 maanden. Patiënten die gemcitabine krijgen, al dan niet gecombineerd met nab-paclitaxel, hebben een mediane overleving van 9 maanden. Wat verder opvalt, is dat er een grote variatie aan behandelingen is ná de standaard eerstelijnsbehandeling met chemotherapie. De data uit dit hoofdstuk zijn van belang omdat ze representatief zijn voor de gehele populatie

met deze aandoening in Nederland. Het geeft bruikbare data om patiënten op een reële wijze te informeren over hun prognose en kansen op een operatie na chemotherapie.

Hoofdstuk 4. De behandeling van oudere patiënten met een lokaal gevorderd pancreascarcinoom

De levensverwachting van de algemene wereldbevolking neemt toe. De associatie tussen leeftijd, behandelstrategie en overleving wordt in dit hoofdstuk beschreven. Patiënten boven de 75 jaar met een lokaal gevorderd pancreascarcinoom, ook met een goede conditie, krijgen minder vaak chemotherapie. Echter, ouderen hebben na correctie voor confounders geen slechtere overleving. Hoewel het moeilijk te onderzoeken is wat de daadwerkelijke overwegingen zijn geweest in het gesprek met de oncoloog waarin werd afgezien van chemotherapie, zou chemotherapie vaker gegeven kunnen worden bij oudere patiënten met een lokaal gevorderd pancreascarcinoom.

Deel II Het voorspellen van uitkomsten

Hoofdstuk 5. Het voorspellen van de overleving en de mogelijkheid tot resectie na FOLFIRINOX

In deel 1 van dit proefschrift wordt beschreven dat een deel van de patiënten met een lokaal gevorderd pancreascarcinoom een chirurgische verwijdering (resectie) kan ondergaan na FOLFIRINOX en dat de overleving erg varieert. Hoofdstuk 5 heeft als doel om een nomogram te ontwikkelen waarmee bij het starten van behandeling voorspeld kan worden wat de kans is op een gunstige uitkomst. Overleving blijkt moeilijk voorspelbaar (c-index 0.61), maar wordt positief beïnvloed door een hogere leeftijd, vrouwelijke geslacht, minder comorbiditeit en een tumormarker CA19.9 ≤274 kU/l. Een mogelijkheid tot resectie wordt voorspeld door de mate van vaatbetrokkenheid bij diagnose en de conditie, uitgedrukt in WHO performance score (c-index 0.79). De beste groep heeft een kans van 35% op een resectie na chemotherapie. Deze waarden kunnen gebruikt worden in het gesprek tussen patiënt en arts waarin de therapiekeuze wordt besproken.

Hoofdstuk 6. Echografie tijdens een operatie om de mogelijkheid tot resectie na FOLFIRINOX te beoordelen

Het selecteren van patiënten die na FOLFIRNOX-chemotherapie in aanmerking komen voor een resectie is moeilijk, omdat een CT-scan vitaal tumorweefsel niet goed kan onderscheiden van verlittekend tumorweefsel na chemotherapie. In dit hoofdstuk wordt een echo gemaakt gedurende de operatie en vergeleken met CT-scans gemaakt voorafgaand aan de operatie. In 32% van de gevallen wordt de mogelijkheid tot resectie van de tumor anders beoordeeld op de echo. De tumor diameter is significant kleiner

bij de operatieve echografie. Echografie helpt echter niet om al voor de operatie patiënten te selecteren die in aanmerking kunnen komen voor een resectie. Nieuwe studies zullen moeten focussen op andere pre-operatieve selectiemethoden zoals een MRI scan, endoscopische echo of het gebruik van biomarkers.

Hoofdstuk 7. Het voorspellen van occulte uitzaaiingen bij patiënten met pancreascarcinoom
Ongeveer 10-20% van de patiënten die worden geopereerd voor een pancreascarcinoom blijkt bij de operatie uitzaaiingen te hebben die vooraf niet worden gezien op beeldvormende onderzoeken. In dit hoofdstuk is gebruik gemaakt van een cohort van 2262 patiënten die in Nederland zijn geopereerd. Het blijkt dat 10% toch uitzaaiingen heeft. Met behulp van data van de Dutch Pancreatic Cancer Audit is een voorspellend model gemaakt. Uitzaaiingen zijn geassocieerd met een hogere leeftijd, een lagere BMI, preoperatieve bijvoeding, een grotere tumor, een veelal solide tumorcomponent (versus cysteus), en onduidelijke afwijkingen op de preoperatieve CT- of MRI-scan. Bij externe validatie in een cohort van 663 patiënten uit Verona (Italië) bleek het model niet goed te voorspellen. Mogelijk zijn biologische factoren meer bepalend dan klinische factoren. Dit zal uit vervolgonderzoek moeten blijken.

Deel III Lokale ablatieve therapieën

Hoofdstuk 8. Geschiktheid voor radiofrequente ablatie en/of irreversibele elektroporatie
Lokale ablatieve behandelingen zijn erop gericht de tumor lokaal zoveel als mogelijk te destrueren zonder dat de tumor operatief wordt verwijderd. Deze methoden worden steeds meer gebruikt in de experimentele setting bij patiënten met een lokaal gevorderd pancreascarcinoom. Twee vergelijkbare methoden, met verschillende onderliggende mechanismen, worden onderzocht in hoofdstuk 8. 91% van de patiënten met een lokaal gevorderd pancreascarcinoom is geschikt voor ten minste één van beide behandelingen. Radiofrequente ablatie (RFA) is meer geschikt voor grotere tumoren, omdat er een veiligheidsmarge tussen de rand van het geableerde gebied en de vitale structuren bewaard moet worden. Irreversibele elektroporatie (IRE) kan vaker bij tumoren die als een manchet om de bloedvaten groeien. Er is ook een significant aandeel van patiënten dat slechts voor één van beide methoden geschikt is (45%). Daarom is het belangrijk om van beide therapieën de veiligheid en effectiviteit verder te onderzoeken.

Hoofdstuk 9. De veiligheid van radiofrequente ablatie bij een lokaal gevorderd pancreascarcinoom
Ter voorbereiding op een gerandomiseerde studie wordt in hoofdstuk 9 de veiligheid van RFA onderzocht. Patiënten die tijdens een operatie zijn gediagnosticeerd met lokaal gevorderde ziekte worden in dezelfde sessie behandeld met RFA. Dit gebeurt echogeleid, door een interventieradioloog, met vooraf afgesproken veiligheidsmarges naar de vitale

organen en bloedvaten. Na de RFA procedure krijgt 46% van de patiënten tijdelijk vertraagde maagontlediging als complicatie. Dit gebeurt meestal bij de patiënten die ook een bypass van de maag naar dunne darm krijgen. Andere grote complicaties treden in deze studie bij 29% van de patiënten op. Fistels van de pancreas, pancreatitis of een perforatie van de darm is bij geen van de patiënten opgetreden. Op basis van deze resultaten wordt RFA als voldoende veilig beoordeeld voor patiënten met een lokaal gevorderd pancreascarcinoom.

Hoofdstuk 10. De PELICAN studie: een gerandomiseerde studie naar de effectiviteit van RFA
Op basis van hoofdstuk 9 wordt een internationale multicenter gerandomiseerde studie ontworpen samen met de multidisciplinaire werkgroep: the Dutch Pancreatic Cancer Group. In dit hoofdstuk wordt het studie protocol beschreven. Patiënten met een lokaal gevorderd pancreascarcinoom, zonder progressie van ziekte na 2 maanden chemotherapie, worden gerandomiseerd tussen wel of geen RFA in combinatie met chemotherapie. De primaire uitkomstmaat is overleving. De studie is gestart in 2015 en de resultaten worden verwacht in 2022.

CONCLUSIE

Het registratie cohort voor patiënten met een lokaal gevorderd pancreascarcinoom uit dit proefschrift geeft realistische gegevens over de overleving en mogelijkheid tot resectie na FOLFIRINOX en andere chemotherapieën. Zeker in een palliatieve setting is het van groot belang om deze resultaten mee te wegen bij de besluitvorming voor het starten van een therapie. Vervolgstudies zullen zich richten op kwaliteit van leven, biomarkers die mogelijke respons op behandeling kunnen voorspellen en het individualiseren van behandelstrategieën. Verder vormt dit proefschrift de basis voor de PELICAN studie, een gerandomiseerde studie naar de effectiviteit van radiofrequente ablatie bij patiënten met een lokaal gevorderd pancreascarcinoom waarvan de resultaten in 2022 verwacht worden.

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LIST OF PUBLICATIONS

1. Brada LJH, Daamen LA, Magermans LG, **Walma MS**, Latifi D, van Dam RM, de Hingh IH, Liem M, de Meijer VE, Patijn GA, Festen S, Stommel MWJ, Bosscha K, Polée MB, Ropela JA, Nio CY, Wessels FJ, de Vries JJJ, van Lienden KP, Bruijnen RC, Busch OR, Groot Koerkamp B, van Eijck C, Molenaar IQ, Wilmink JW, van Santvoort HC, Besselink MG for the Dutch Pancreatic Cancer Group. Survival benefit associated with resection of locally advanced pancreatic cancer following upfront FOLFIRINOX versus FOLFIRINOX only: multicenter propensity score-matched analysis. *Annals of Surgery.* 2021 Jul 29. Epub ahead of print. PMID: 34334641

2. Brada LJH, **Walma MS**, Daamen LA, van Roessel S, van Dam RM, de Hingh IH, Liem MS, de Meijer VE, Patijn GA, Festen S, Stommel MWJ, Bosscha K, Polée MB, Nio CY, Wessels FJ, de Vries JJJ, van Lienden KP, Bruijnen RC, Los M, Haj Mohammad N, Wilmink JW, Busch OR, Besselink MG, Molenaar IQ, van Santvoort HC for the Dutch Pancreatic Cancer Group. Predicting overall survival and resection in patients with locally advanced pancreatic cancer treated with FOLFIRINOX: development and internal validation of two nomograms. *Journal of Surgical Oncology.* 2021 Sep;124(4):589-597.

3. **Walma MS**, Rombouts SJ, Brada LJH, Borel Rinkes IH, Bosscha K, Bruijnen RC, Busch OR, Creemers GJ, Daams F, van Dam RM, van Delden OM, Festen S, Ghorbani P, de Groot DJ, de Groot JWB, Haj Mohammad N, van Hillegersberg R, de Hingh IH, D'Hondt M, Kerver ED, van Leeuwen MS, Liem MS, van Lienden KP, Los M, de Meijer VE, Meijerink MR, Mekenkamp LJ, Nio CY, Oulad Abdennabi I, Pando E, Patijn GA, Polée MB, Pruijt JF, Roeyen G, Ropela JA, Stommel MWJ, de Vos-Geelen J, de Vries JJ, van der Waal EM, Wessels FJ, Wilmink JW, van Santvoort HC, Besselink MG, Molenaar IQ; Dutch Pancreatic Cancer Group. Radiofrequency ablation and chemotherapy versus chemotherapy alone for locally advanced pancreatic cancer (PELICAN): study protocol for a randomized controlled trial. *Trials.* 2021 Apr 29;22(1):313.

4. Brada LJH, **Walma MS,** van Dam RM, de Vos-Geelen J, de Hingh IH, Creemers GJ, Liem MS, Mekenkamp LJ, de Meijer VE, de Groot DJA, Patijn GA, de Groot JWB, Festen S, Kerver ED, Stommel MWJ, Meijerink MR, Bosscha K, Pruijt JF, Polée MB, Ropela JA, Cirkel GA, Los M, Wilmink JW, Haj Mohammad N, van Santvoort HC, Besselink MG, Molenaar IQ; Dutch Pancreatic Cancer Group. The treatment and survival of elderly patients with locally advanced pancreatic cancer: A post-hoc analysis of a multicenter registry. *Pancreatology*. 2021 Jan;21(1):163-169.

5. **Walma MS,** Brada LJ, Patuleia SIS, Blomjous JG, Bollen TL, Bosscha K, Bruijnen RC, Busch OR, Creemers GJ, Daams F, van Dam R, Festen S, Jan de Groot D, Willem de Groot J, Mohammad NH, Hermans JJ, de Hingh IH, Kerver ED, van Leeuwen MS, van der Leij C, Liem MS, van Lienden KP, Los M, de Meijer VE, Meijerink MR, Mekenkamp LJ, Nederend J, Nio CY, Patijn GA, Polée MB, Pruijt JF, Renken NS, Rombouts SJ, Schouten TJ, Stommel MWJ, Verweij ME, de Vos-Geelen J, de Vries JJJ, Vulink A, Wessels FJ, Wilmink JW, van Santvoort HC, Besselink MG, Molenaar IQ; Dutch Pancreatic Cancer Group. Treatment strategies and clinical outcomes in consecutive patients with locally advanced pancreatic cancer: A multicenter prospective cohort. *Eur J Surg Oncol*. 2021 Mar;47(3 Pt B):699-707.

6. van Veldhuisen E, van den Oord C, Brada LJ, **Walma MS**, Vogel JA, Wilmink JW, Del Chiaro M, van Lienden KP, Meijerink MR, van Tienhoven G, Hackert T, Wolfgang CL, van Santvoort H, Groot Koerkamp B, Busch OR, Molenaar IQ, van Eijck CH, Besselink MG; Dutch Pancreatic Cancer Group and International Collaborative Group on Locally Advanced Pancreatic Cancer. Locally Advanced Pancreatic Cancer: Work-Up, Staging, and Local Intervention Strategies. *Cancers (Basel)*. 2019 Jul 12;11(7):976.

7. **Walma MS,** Fegrachi S, de Vries JJJ, van Santvoort HC, Besselink MG, von Asmuth EG, van Leeuwen MS, Borel Rinkes IH, Bruijnen RC, de Hingh IH, Klaase JM, Molenaar IQ, van Hillegersberg R. Safety of radiofrequency ablation in patients with locally advanced, unresectable pancreatic cancer: A phase II study. *Eur J Surg Oncol.* 2019 Nov;45(11):2166-2172.

8. **Walma MS,** van Veldhuisen E, van Rijssen LB, Busch OR, Bruijnen RCG, van Delden OM, Mohammad NH, de Hingh IH, Yo LS, van Laarhoven HW, van Leeuwen MS, Nio CY, van Santvoort HC, de Vries J, Wessels FJ, Wilmink JW, Molenaar IQ, Besselink MG, van Lienden KP; Dutch Pancreatic Cancer Group. Added value of intra-operative ultrasound to determine the resectability of locally advanced pancreatic cancer following FOLFIRINOX chemotherapy (IMAGE): a prospective multicenter study. *HPB (Oxford)*. 2019 Oct;21(10):1385-1392.

9. Rombouts SJE, Derksen TC, Nio CY, van Hillegersberg R, van Santvoort HC, **Walma MS**, Molenaar IQ, van Leeuwen MS. Computed tomography findings after radiofrequency ablation in locally advanced pancreatic cancer. *Abdom Radiol (NY)*. 2018 Oct;43(10):2702-2711.

10. Van Veldhuisen E, Brada LJ, **Walma MS,** Molenaar IQ, van Lienden KP, Wilmink JW, Besselink MG, Busch OR. Resectie van lokaal gevorderd pancreascarcinoom na

inductie FOLIRINOX chemotherapie: nieuwe ontwikkelingen. *Ned Tijd v Oncol*. 2018;15;290-6.

11. van Rijssen LB, Rombouts SJ, **Walma MS**, Vogel JA, Tol JA, Molenaar IQ, van Eijck CH, Verheij J, van de Vijver MJ, Busch OR, Besselink MG; Dutch Pancreatic Cancer Group. Recent Advances in Pancreatic Cancer Surgery of Relevance to the Practicing Pathologist. Surg Pathol Clin. 2016 Dec;9(4):539-545.

12. Walma MS, Rombouts SJ, Vogel JA, van Rijssen LB, Wilmink JW, Mohammad NH, van Santvoort HC, Molenaar IQ, Besselink MG. Systematic Review of Resection Rates and Clinical Outcomes After FOLFIRINOX-Based Treatment in Patients with Locally Advanced Pancreatic Cancer. *Ann Surg Oncol.* 2016 Dec;23(13):4352-4360

13. Walma MS, Rombouts SJ [..] Besselink MG, Molenaar IQ; Dutch Pancreatic Cancer Group. Radiofrequente ablatie van het lokaal irresectabel pancreascarcinoom en de mogelijkheid tot een resectie na inductie chemotherapie: de PELICAN studie. *Ned Tijd v Oncol*. 2016;13;91-4.

14. Kornmann VN, **Walma MS,** de Roos MA, Boerma D, van Westreenen HL. Quality of Life After a Low Anterior Resection for Rectal Cancer in Elderly Patients. *Ann Coloproctol.* 2016 Feb;32(1):27-32.

15. Walma MS, Burbach JP, Verheijen PM, Pronk A, van Grevenstein WM. Vacuum-assisted closure therapy for infected perineal wounds after abdominoperineal resection. A retrospective cohort study. *Int J Surg.* 2016 Feb;26:18-24.

16. Walma MS, Kornmann VN, Boerma D, de Roos MA, van Westreenen HL. Predictors of fecal incontinence and related quality of life after a total mesorectal excision with primary anastomosis for patients with rectal cancer. Ann Coloproctol. 2015 Feb;31(1):23-8.

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Alle UMCU collega onderzoekers – Stafleden uit het UMCU – Stafleden uit het Meander MC – collega's uit het Meander MC – AMC onderzoekers – Secretaresses: Fatiha, Mariëlle, Romy – Annemarie Roele – IKNL – Alle research nurses in alle PELICAN centra – Mijn schoonfamilie – De Toren – MeidenMijdag – Heelkunde chicks for life – Bestuur 10-11 – Schoonhoven vrienden – Vocus – Touché – LMSG – Eetclub – Schmetterlingen – Hardloopgroep Runxperience – Zwembad Kromme Rijn – Amelisweerd – Broodje Ben – Pitstop – Back&Fourth – de Voortuin – Thuisbezorgd.nl

Tot slot de belangrijkste: **Frederik**, bedankt voor alles, voor altijd.

CURRICULUM VITAE AUCTORIS

Marieke Suzanne Walma was born on the 26th of October 1988 in Gouda, the Netherlands. She grew up with her parents and sister in Schoonhoven, alongside the Lek river. After graduating cum laude from the CSG Willem de Zwijger Schoonhoven, she started Medical School at Utrecht University in 2006. Marieke combined medical school with being an active member of the student rowing association U.S.R. "Triton". From September 2010 until September 2011 she took a gap year to be a full-time member of the board of her student association as treasurer.

After graduating from Medical School in December 2013, Marieke started clinical work as a resident not in training at the Department of Surgery at the University Medical Center Utrecht. In July 2015 she started a PhD-track on locally advanced pancreatic cancer at the Department of Surgery under the supervision of Prof. dr. I.Q. Molenaar and Prof. dr. M.G. Besselink. She coordinated a randomized controlled trial (PELICAN trial) and initiated the study internationally. The study was rewarded by a grant from the Dutch Cancer Society (KWF). The results of this study are expected soon.

Marieke her biggest hobby is running. She often interrupted her working days for a run through Amelisweerd, a nature reserve next to the University Medical Center Utrecht. Together with the organization 'Run for Life', Marieke ran the New York Marathon in 2017 and together they raised money for the Dutch Cancer Society. Afterwards she also completed the Berlin Marathon and Rotterdam Marathon during her time as researcher.

Marieke currently lives with Frederik in Utrecht and is working as surgical resident in training at the Meander Medical Center in Amersfoort under the supervision of dr. V. van Weel.


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